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Current results of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)

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Complete List of Authors:	<p>Onorati, Francesco; Div Cardiac Surgery, Surgery - University of Verona Medical School</p> <p>Gherli, Riccardo; Hospital S. Camillo-Forlanini, Rome, of Cardiosciences</p> <p>Mariscalco, Giovanni; University Hospitals of Leicester NHS Trust, Department of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital</p> <p>Girdauskas, Evaldas; University Heart Center Hamburg, Hamburg, Germany</p> <p>Quintana, Eduardo; University Hospital Clinic,</p> <p>Santini, Francesco; Cardiac Surgery Unit, University of Genova</p> <p>De Feo, Marisa; V. Monaldi Hospital</p> <p>Sponga, Sandro; Cardiothoracic Department, University Hospital of Udine</p> <p>Tozzi, Piergiorgio; Centre Hospitalier Universitaire Vaudois,</p> <p>Bashir, Mohamad; St. Barth Hospital NHS,</p> <p>Anttila, Vesa; Turku University Hospital, University of Turku,</p> <p>Perrotti, Andrea; University Hospital Jean Minjoz,</p> <p>Pappalardo, Aniello; Ospedali Riuniti</p> <p>Biancari, Fausto; Oulu University Hospital, Department of Surgery</p> <p>Ruggieri, Vito; Pole TCVN, Hopital Robert Debrè</p> <p>Rinaldi, Mauro; Torino University Hospitals</p> <p>Antona, Carlo; Ospedale Luigi Sacco-Polo Universitario</p> <p>Nicolini, Francesco; University of Parma</p>
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Current results of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)

F. Onorati¹, R. Gherli², G. Mariscalco³, E. Girdauskas⁴, E.O. Quintana⁵, F. Santini⁶, M. De Feo⁷, S. Sponga⁸, P. Tozzi⁹, M. Bashir¹⁰, V. Anttila¹¹, A. Perrotti¹², A. Pappalardo¹³, F. Biancari¹⁴, V.G. Ruggieri¹⁵, M. Rinaldi¹⁶, C. Antona¹⁷, F. Nicolini¹⁸, on behalf of E-AVR Collaborators.

¹Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; ²Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy; ³Department of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK; ⁴Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany; ⁵University Hospital Clinic, Barcellona, Spain; ⁶Cardiac Surgery Unit, University of Genova, Genoa, Italy; ⁷Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy; ⁸Cardiothoracic Department, University Hospital of Udine, Udine, Italy; ⁹Cardiac Surgery Unit, Centre Hospitalier Universitaire Vaudois, Lausanne; ¹⁰Division of Cardiac Surgery, St. Barth Hospital NHS, London, UK; ¹¹Heart Center, Turku University Hospital, University of Turku, Turku, Finland; ¹²Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France; ¹³Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy; ¹⁴Department of Surgery, Oulu University Hospital, Oulu, Finland; ¹⁵Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN, Hopital Robert Debre', Reims, France; ¹⁶Department of Cardiac Surgery, Torino University Hospitals, Turin, Italy; ¹⁷Department of Cardiac Surgery, Ospedale Sacco, Milan, Italy; ¹⁸Cardiac Surgery Unit, University of Parma, Parma, Italy

Corresponding Author: Francesco Onorati, MD PhD – Div. Cardiac Surgery, Dpt. of Surgery, University of Verona Medical School - Piazzale Stefani n.1 – 37126 – Verona, Italy. Phone: 0039 (0)45 8121945; Fax: 0039 (0)45 8123308; Email: francesco.onorati@aovr.veneto.it

ABSTRACT

Introduction: Traditional and transcatheter surgical treatments of severe aortic valve stenosis (SAVS) are increasing in parallel with the improved life-expectancy. Recent randomized trials (RCTs) reported comparable or non-inferior mortality with transcatheter treatments compared to traditional surgery. However, RCTs have the limitation of being a mirror of the predefined inclusion/exclusion criteria, without reflecting the “real clinical world”.

Technological improvements have recently allowed the development of minimally invasive surgical accesses and the use of sutureless valves, but their impact on the clinical scenario is difficult to assess because of the monocentric design of published studies and limited sample-size. A prospective multicentre registry including all patients referred for a surgical treatment of SAVS (traditional, through full-sternotomy; minimally-invasive; or transcatheter; with both “sutured” and “sutureless” valves) will provide a “real-world” picture of available results of current surgical options, and will help to clarify the “grey zones” of current guidelines.

Methods and analysis: E-AVR is a prospective observational open registry designed to collect all data from patients admitted for SAVS, with or without coronary artery disease, in 18 cardiac surgery Centres located in seven countries (Finland, France, Germany, Italy, Spain, Switzerland, and United Kingdom). Patients will be enrolled over a 2-year period and followed-up for 5 years after enrolment. Outcome definitions are concordant with VARC-2 criteria and established guidelines. Primary outcome is 30-day cardiovascular mortality, with secondary “early” outcomes aimed at establishing concurrent cardiac and major organ comorbid-complications. Follow-up secondary outcomes are all-cause and cardio-vascular mortality, major morbidity, structural and non-structural valve complications, quality of life and echocardiographic data.

Ethics and dissemination: The study protocol is approved by Local Ethics Committees. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship.

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STRENGTHS AND LIMITATIONS OF THIS STUDY:

- The protocol addresses the important question of which surgical treatment offers the most benefits in the management of patients with severe aortic valve stenosis, with or without concomitant coronary artery disease.
- The expected large sample size will guide sub-analyses aimed at identify specific patient characteristics and different risk-profiles, which are better served with alternative surgical techniques.
- The 5-year follow-up will provide definite answers about the long-term safety and efficacy of recent surgical innovations (i.e. sutureless valves, minimally invasive approaches, surgical TAVR), whose long-term follow-up data are still lacking in current literature
- The present multicentre registry has clearly established aim, inclusion and exclusion criteria, short-term and follow-up primary and secondary endpoints, as well as state-of-the-art methods for data collection and endpoints definition
- Limitations include variations in postoperative and follow-up management, which are based on local Institutional policies, and lack of blinding between the central statistical core-lab performing the analyses and the employed surgical techniques

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INTRODUCTION

The prevalence of severe aortic valve stenosis (SAVS) correlates with age, and its treatment is expected to increase parallel to the improved life-expectancy reported in Western Countries (1-2). Traditional surgical aortic valve replacement (SAVR) has been the gold standard of treatment for decades, with well-documented benefits in terms of symptom improvement and survival (3-4). Recent technological advances allowed interventional and surgical transcatheter aortic valve replacements (TAVR), which proved to be effective alternatives to traditional SAVR, in both high-risk and intermediate-risk patients (5-12). Therefore, SAVR and TAVR represent nowadays the standard surgical armamentarium for aortic valve replacement.

Alternative surgical approaches, based on the concept of TAVR (13,14), have in fact been developed. In particular, there are on the market a number of “sutureless” valves, aimed at reducing some surgical drawbacks, such as cross-clamp time with corresponding myocardial ischemia-reperfusion injury (13,15-20). Moreover, different mini-thoracotomy and mini-sternotomy approaches to SAVR have been widely adopted by the surgical community - with both “sutured” and “sutureless” valves - in order to reduce surgical trauma, systemic inflammatory response, and major organ morbidity (13,15,16). Various different combinations of minimally invasive accesses and the use of last-generation valves have been reported to date (14,17,18). But despite early enthusiasm about preliminary results with these technological improvements, none of these techniques has yet replaced traditional SAVR in standard surgical practice, mainly because reporting of results of these alternative techniques tends to be biased by single-centre design, limited sample-size, and the strict inclusion/exclusion criteria of the published studies (13,14).

Another “hot topic” in this debate relates to valve durability, given that the long-term durability of both TAVR and sutureless valves is as yet unknown. Indeed, standard “sutured” surgical valves demonstrated excellent durability, both in the very-long term and in very-young adults below the 65-year cut-off age (21-23), which is still the threshold for biological valves recommended by European Society of Cardiology (ESC) / European Association for CardioThoracic Surgery

(EACTS) guidelines (24). This issue is of particular interest, given that the use of TAVR has increased in younger intermediate-risk patients, despite recent caveats relating to early degeneration of TAVR (25,26).

Similarly, improved life-expectancy has led to a growing number of patients with degenerated dysfunctioning aortic bioprostheses requiring surgical treatment. Again, surgical aortic prosthetic replacement (SAPR) has been traditionally considered the only treatment strategy for these patients, given the excellent results, recently confirmed by several studies (27,28). Again, transcatheter treatments (“valve-in-valve”) have recently demonstrated comparable or sometimes superior results in redo-scenarios (29). Therefore, data on the efficacy, safety and durability of these technological improvements are essential for providing “strong” statements in future guidelines, and for evaluating the extension of these techniques to low-risk and young patients in the future.

Finally, it is well known that critical coronary artery disease (CAD) often coexists with SAVS.

Although the standard treatment option for these patients has traditionally been SAVR plus coronary artery bypass grafting (CABG), the introduction of TAVR and minimally invasive surgical alternatives has considerably changed the available options, paving the way to combined less-invasive SAVR+CABG and/or TAVR±PCI (either before, during or after the surgical procedure) (30-34). Again, there is a great deal of confusion on the topic, and there are unanswered questions on the efficacy and safety of these options, as well as on what to expect from late follow-up when compared to the standard practice of SAVR+CABG.

Robust early and follow-up data on the safety and efficacy of surgical TAVR, last-generation sutureless surgical valves, and minimally-invasive approaches compared with standard SAVR, with or without a contemporary (surgical or interventional) treatment of concurrent CAD, are still lacking for a real-world large population of patients at variable surgical risk. Such data is urgently required for the correct allocation of therapy in daily surgical practice. Furthermore, data on quality of life and functional echocardiographic results with different surgical alternatives might similarly help physicians in decision-making in local “Heart Teams”. Data from a multicentre, real-world,

open registry enrolling all patients with SAVS±CAD consecutively referred to several Centres at different European latitudes should help to answer some of these open questions. Here, we describe the rationale and the study protocol of the European Aortic Valve Registry (E-AVR), a multicenter prospective open registry on aortic valve surgical practice.

METHODS AND ANALYSIS

Rationale of the study

Improvements in surgical treatment of cardiac diseases can be obtained with the implementation of current techniques and the development of new methods, based on information from large clinical datasets (35). The main strength of a prospective clinical open registry is the high external validity, given that data are collected in the settings of standard clinical practice. Moreover, large sample size enables a better estimation of event rates, and allows the investigation of hard endpoints and outcomes, by means of a wide population of patients from different institutions and with extremely limited exclusion criteria.

Importantly, clinical registries may provide data on long-term outcomes occurring after the study period of a trial (35). They are more practical than randomized controlled trials, require fewer resources, and have less stringent inclusion and exclusion criteria for patient enrolment. Finally, clinical findings from registries have even more significance when patient-populations derive from different geographic areas, with heterogeneous referral pathways, baseline clinical characteristics, and perioperative treatment strategies. All these features substantiate the concept of “a real world practice” underlying any “registry-study”.

Therefore, the rationale of this European multicenter observational open registry is to prospectively collect data on baseline characteristics, treatment options, perioperative management and postoperative outcome of all patients consecutively undergoing surgical treatment of SAVS±CAD at 18 European university or non-university tertiary hospitals located in seven European countries

(Finland, France, Germany, Italy, Spain, Switzerland, and United Kingdom). The complete list of E-AVR Collaborators is reported in the Appendix.

For the purpose of this study, patients will be consecutively enrolled for a 2-year period, and will be followed-up for 5 years after the index surgical treatment.

The following surgical options will be considered:

- 1) SAVR with mechanical valves
- 2) SAVR with biological valves (either sutured or sutureless, stented or stentless)
- 3) Surgical TAVR (either transapical, trans-axillary, or transaortic)

Similarly, the following surgical approaches will be considered:

- 1) Full sternotomy
- 2) Mini-thoracotomy (either left-sided for TAVR or right-sided for SAVR)
- 3) Partial-sternotomy

A flow-chart of the enrolment criteria and of the surgical techniques considered in the registry is provided in Figure 1.

Criteria for registry-enrolment

The following inclusion and exclusion criteria will be considered:

Inclusion criteria

- Patients aged >18 years
- Primary or repeat surgical treatment of SAVS, with or without associated CABG
- Reoperation for any aortic prosthetic dysfunction

Exclusion criteria

- Patients undergoing concomitant mitral valve surgery, or tricuspid valve surgery, or aortic surgery or any other associated cardiac surgical procedure (with the exception of CABG)
- Porcelain aorta

Patients will be recruited in a consecutive series from each institution, and their data collected in a dedicated on-line datasheet. The recruitment period will be 24 months, from 1st October 2017 to

30th September 2019. Every patient will be followed up at 30 days, 6 months, 1 year, and yearly thereafter up to 5 years after the index surgical procedure (Figure 2). On the basis of historical cohort data of local institutions, we expect to enrol a minimum of 4000 patients at the end of the first year, and a minimum of 8000 patients at the end of enrolment.

Informed consent

Written informed consent will be obtained from the patient or patient’s authorized representative prior to enrolment in the Registry. The study will be conducted in accordance with the provisions of the Declaration of Helsinki. The study is registered in Clinicaltrials.gov. (No. NCT03143361)

Data management and monitoring

Data will be collected into a dedicated datasheet with predefined variables. Storage, analysis and auditing of data will be accomplished by an independent Central Core Laboratory. Auditing of the dataset will be performed every six months by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator for further data checking and merging. The merged and checked dataset will be available to all E-AVR researchers for analysis and interpretation of data.

Statistical methods

An independent central statistical Core Lab will perform all the statistical analyses derived from this registry.

Continuous variables will be reported as mean and standard deviation or median and interquartile range, as appropriate. 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, Kruskal-Wallis test, Wilcoxon test, Fisher exact test, Chi-square test and Kaplan-Meier test. Multivariable analyses will be performed using logistic, classification tree, linear and ordinal regression methods as well as the Cox-proportional hazards method. Significant differences between study groups will be adjusted by using propensity score as covariate or by one-to-one propensity score matching. Matching will be performed using a caliper width of 0.2 of the standard

deviation of logit of the propensity score. Multiple propensity score adjusted analysis will be performed in case of multiple study groups. A Bayesian hierarchical approach will be used in the case of significant variability between centres.

Missing values will be replaced and estimated using multiple imputations. Furthermore, sensitivity analysis will be executed using complete-case analysis. Interim analyses are planned at 1 year after the enrolment of the first patient, and at completion of the first year and the third year of follow-up of the last enrolled patient.

Early and late endpoints

Outcome endpoints will be defined according to current guidelines, i.e. VARC-2 definitions (36) and Guidelines for reporting mortality and morbidity after cardiac valve interventions (37).

In more detail, the following outcome variables will be collected:

Primary outcome of the E-AVR registry: 30-day cardiovascular mortality

Secondary outcomes of the E-AVR registry: these will be dichotomized into “early” at 30-day (i.e. during hospitalization, at home if discharged, or during “rehab-hospitalization” at any time point if never discharged home) and “late” (after the patient is discharged home):

- 1) Early secondary outcomes: all-cause mortality, stroke, acute myocardial infarction (AMI) (38), postoperative need for prolonged use of inotropes (>72 hours), postoperative need for intra-aortic balloon pump (IABP) or extracorporeal mechanical oxygenation (ECMO), surgical site infection, blood losses and use of blood products (during hospitalization for the index surgical procedure), nadir hematocrit, nadir hemoglobin, re-sternotomy for bleeding, atrial fibrillation (first event and number of events), cardiac conduction disturbances, need for new permanent pace-maker implantation, acute kidney injury (following AKIN classification), pericardial effusion requiring treatment, length of stay in the intensive care unit, length of in-hospital stay (for the index procedure), device success, early safety, clinical efficacy, time-related valve safety, echocardiographic data of prosthesis performance, early

repeat surgery for failure of the index procedure (any “redo” before discharge home or to rehabilitation clinic).

- 2) Late secondary outcomes (collected starting from discharge to the end of the 5th year after the index procedure): all-cause mortality, cardiovascular mortality, stroke, acute myocardial infarction, reintervention on the aortic prosthesis, repeat revascularization (either with percutaneous coronary intervention or CABG), prosthetic thrombosis, embolism, bleeding events, structural valve deterioration, paravalvular leakage, prosthetic endocarditis, need for permanent pacemaker, need for implantable cardioverter-defibrillator, MACCE (defined as a composite end-point including any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, repeated revascularization), time-related valve safety, quality of life (QoL; defined according to Short Form-8 questionnaire; QoL will be assessed during follow-up visits at outpatient clinics or, if other methods are not possible, by telephone interview); echocardiographic data of prosthesis performance.

Echocardiographic data of prosthesis performance are defined according to the Valve Academic Research Consortium-2 definitions (36). These outcomes and their definition criteria are described in detail in the following sections of this article.

Data collection

Units of measurement: Laboratory data will be collected according to fixed units of measurement in order to avoid any problem stemming from differences in units used by the various participating centres, during data merging and analysis. The fixed units of measurement are reported in the dedicated CRF datasheet.

Laboratory parameters: baseline levels of haemoglobin, haematocrit, platelets, blood glucose, HbA1c, C-reactive protein, TT-INR and albumin will be collected.

Hypertension: arterial blood pressure > 140/90 mmHg or anti-hypertensive treatment.

Diabetes: diabetes mellitus requiring diet, oral or insulin treatment.

Preoperative creatinine levels: this parameter is obtained on the day before surgery and is expressed in $\mu\text{mol/L}$.

Chronic Kidney Disease: the severity of renal failure will be classified as shown in Table 1. It is stratified by the estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease Study Group modified formula (39). eGFR for calculation of the EuroSCORE II (40) will be estimated using the Cockcroft-Gault formula (41) according to the criteria of this risk scoring method.

Dialysis: peritoneal or hemo-dialysis before surgery.

Chronic obstructive pulmonary disease (COPD): any long-term use of bronchodilators or steroids for lung disease.

Oxygen therapy: long-term oxygen therapy for respiratory failure.

Liver disease: different degrees of liver failure stratified according to the Child-Pugh classification (42).

Active neoplasia: any active malignancy.

Preoperative stroke: any preoperative focal or global neurological syndrome caused by ischemia or haemorrhage not resolving within 24 hours.

Neurological dysfunction: disabling outcomes in ambulation and / or normal motor functions, according to EuroSCORE II definition (40).

Extracardiac arteriopathy: one or more of the following: claudication, carotid occlusion or >50% stenosis, amputation for arterial disease, previous or planned intervention on the abdominal aorta, limb arteries or carotids.

Preoperative ECG: sinus rhythm, or atrial fibrillation; or first degree AV block; or right bundle block; or left bundle block; or pacemaker rhythm.

Preoperative myocardial infarction: any preoperative myocardial infarction.

Previous vascular surgery: history of surgical or endovascular procedure of the thoracic or abdominal aorta and/or the iliac-femoral arteries.

Previous cardiac surgery: one or more previous cardiac operations requiring opening of the pericardium.

Type of previous cardiac surgery: description of previous cardiac operation.

Previous aortic valve replacement: description of prosthesis and date of operation.

Previous percutaneous coronary intervention: any previous percutaneous coronary intervention.

Etiology of aortic valve disease: native valve disease (degenerative; rheumatic; endocarditic) or prosthetic valve disease.

Endocarditis: any diagnosis of valve endocarditis made by the Heart Team and/or antibiotic treatment for endocarditis at the time of surgery. Subclassification into acute, subacute, and healed endocarditis based on Current Guidelines will be added (43).

Endocarditis etiology: microbe isolated for the diagnosis of endocarditis

NYHA functional classes: defined according to the criteria listed in Table 2 (44).

Aortic valve stenosis: severity of aortic valve stenosis before surgery will be graded as moderate or severe according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (45).

Aortic valve regurgitation: Severity of aortic valve regurgitation before surgery will be graded in classes from 0 to 3, and the grade of severity will be evaluated according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (45).

Associated critical coronary artery disease: presence of stenosis of at least 70% in any major epicardial coronary artery. Number of main vessels involved will be recorded. Patients with stenosis of the left main coronary artery will be considered as having at least two-vessel disease.

Associated left main coronary artery disease: Any LMSD > 50%

Mitral valve regurgitation: severity of concurrent mitral valve regurgitation - though not requiring surgery - will be graded in classes according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (45).

Left ventricular function: last measured left ventricular ejection fraction before surgery (in any case before induction of anesthesia).

Pulmonary hypertension: absent: <31 mmHg; moderate: 31-55 mmHg; severe: >55 mmHg, according to EuroSCORE II definition (40). Systolic pulmonary pressure will be estimated at echocardiography, at least before induction of anesthesia.

Preoperative echocardiography data: aortic valve area, peak transvalvular gradient, mean transvalvular gradient, aortic annulus diameter, maximum jet velocity (TTE) will be recorded.

Preoperative multislice CT scan data: annulus circumference; valvular area; calcium score (collected for all surgical TAVR, and only if available for other surgical techniques)

Diseased ascending aorta: any sign of diffuse atherosclerosis in the ascending aorta at palpation or epiaortic ultrasound (porcelain aorta is not considered).

Montgomery classification: if available, echocardiographic Montgomery classification of aortic atheromas will be provided.

Preoperative antithrombotic or antibiotic drug treatment: data on all antithrombotic drugs administered before surgery will be collected. The date of pause of drug treatment is the last day the patient received the drug. Data on any oral or intravenous antibiotics administered preoperatively without prophylaxis purpose, i.e. for any preoperative infectious condition, will be collected.

Elective surgery: elective procedure scheduled for stable aortic valve disease.

Urgent surgery: procedure indicated by medical factors which require the patient to stay in hospital to have operation before discharge.

Emergency surgery: procedure performed before the beginning of the working day after the decision to operate.

Frailty: Preoperative patient's frailty is graded according to Geriatric Status Scale, as proposed by Rockwood et al (46).

Critical preoperative status: ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anesthetic room, preoperative inotropes or IABP, preoperative acute renal failure (anuria or oliguria <10ml/hr), according to EuroSCORE II definition (40).

EuroSCORE II: this risk score is calculated using the on-line calculator available at <http://www.euroscore.org/calc.html> and reported as a percentage. The risk factors included in the EuroSCORE II and collected in the E-AVR registry are defined according to the EuroSCORE II criteria (40).

STS score: this risk score is calculated using the on-line calculator available at <http://riskcalc.sts.org/stswebriskcalc/#/> and reported as a percentage. The risk factors included in the STS score and collected in the E-AVR registry are defined according to the STS score criteria (47).

Surgical chest access: classified as 1) full sternotomy; 2) minithoracotomy; 3) partial-sternotomy.

Aortic valve replacement data: classified as 1) mechanical prosthesis; 2) stented biological prosthesis; 3) stentless biological prosthesis; 4) sutureless biological prosthesis; 5) trans-apical TAVR; 6) transaortic TAVR. The description of model and diameter of the prosthesis implanted and possible need for proctored procedure will also be collected.

Other intraoperative data: type of cardioplegia and its temperature, duration of extracorporeal circulation (ECC), nadir temperature of ECC, and aortic cross-clamping time, need for re-aortic

cross-clamping for any reason (paravalvular leak, coronary obstruction, annular rupture/hematoma, re-construction of CABG, etc), as well as details of TAVR implantation including sheath size, pre-implantation valvuloplasty, occurrence of valve-in-valve emergency procedure, the number of valves implanted, prosthesis migration, recapturing and re-positioning of the valve, post-procedural dilation, amount of contrast medium administered will be collected.

CABG details: Details of types of conduit and target vessel will be reported (e.g.: LIMA-LAD, RIMA-Dx, RA-MO. SV-DIAG): The following specifications for conduits will be used: LIMA: left internal mammary artery; RIMA: right internal mammary artery; RA: radial artery; GEA: gastro-epiploic artery; SV: saphenous vein. The following target acronyms will be used: DA: anterior descending; DIAG: diagonal; RX: right coronary (trunk); PDA: posterior descending; PL: postero-lateral; OM: obtuse marginal. In the event of sequential grafting, the prefix "seq" will be used before targets (e.g. LIMA-seq DIAG-DA)

Other CABG details: number of distal anastomoses, completeness of revascularization.

30-day cardiovascular mortality: based on VARC-2 definition (36) and occurring within 30-days or during hospitalization for the index procedure if the postoperative length of stay is longer than 30 days. This includes: 1) death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure, low cardiac output syndrome, etc.); 2) death caused by non-coronary vascular conditions (e.g. pulmonary embolisms, stroke, aortic rupture or vascular dissection, etc); 3) all procedure-related deaths (including those related to a complication of the procedure or a treatment for a complication of the procedure); 4) all valve-related deaths including valve dysfunction (structural or non-structural) and other valve-related adverse events; 5) sudden or unwitnessed death

30-day all-cause mortality: defined as the sum of cardiovascular and non-cardiovascular, the latter defined as any death in which the primary cause is clearly related to another condition not contemplated by the definition "cardiovascular" (e.g. trauma, cancer, etc.), as in VARC-2 definition

(36), but occurring within 30-days or during index procedure hospitalization if the postoperative length of stay is longer than 30 days.

Type 5 myocardial infarction: defined according to the recent criteria defined by Moussa et al. (48) (Table 3).

Atrial fibrillation: any new paroxysmal/permanent atrial fibrillation episode requiring or not requiring pharmacological or electrical cardioversion attempts. Number of recurrences will be also collected.

Cardiac conduction disturbances: defined as a new left bundle branch block, right bundle branch block, or AV-block (1st, 2nd or 3rd degree). Diagnosis will be based on official medical reports from a consultant cardiologist. In case of progressive bradi-arrhythmias, the evolution of the arrhythmias will be collected.

Need for permanent PMK: collected as a dichotomic variable. Type of permanent pacing set-up (e.g. AAI, VVI, DDD, etc) will be collected.

Postoperative neurologic damage: classified as: 0) absent; 1) disabling stroke; 2) non-disabling stroke; 3) TIA, based on definitions of VARC-2 consensus (36).

Stroke classification: 1) ischemic; 2) haemorrhagic; 3) unknown, according to VARC-2 consensus (36). The diagnosis and nature of stroke will be supported by CT or MRI imaging and confirmed by a consultant neurologist.

Prolonged use of inotropes (>72 hours): This refers to the use of inotropes for >72 hours after the index operation. The type, dose and duration of administered inotropes will be also collected.

Cardiogenic shock: postoperative critical hemodynamic condition requiring mechanical ventricular-assist devices or high-dose inotropes with evidence of peripheral malperfusion. Coexistence of a cardiac index < 1.8 l/min/m² despite adequate correction of all the coexisting preload, afterload, electrolyte and gas-analyses abnormalities will be pursued with the aid of different hemodynamic monitoring methods, according to local Institutional policies (e.g. echocardiography, Swan-Ganz catheter, PICCO, PRAM, Vigileo, etc.).

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3 *IABP*: intra- or postoperative insertion of an intra-aortic balloon pump device.

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5 *ECMO*: intra- or postoperative insertion of an extracorporeal mechanical pump/oxygenation device.

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7 *Bleeding*: classified as 1) life-threatening or disabling bleeding; 2) major bleeding; 3) minor
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9 bleeding, according to the recent definition criteria reported by the VARC-2 document (36).

10
11 *Blood loss 12 hours after surgery*: the amount of postoperative blood losses from mediastinal
12
13 drainages 12 hours after surgery. Intraoperative blood losses are not taken into account. Nadir
14
15 haemoglobin and nadir haematocrit will be collected.

16
17
18 *No. of transfused RBC units at hospital discharge*: total amount of RBC units intra- and/or
19
20 postoperatively transfused, from the beginning of surgery to the day of discharge.

21
22 *No. of transfused fresh frozen plasma, pooled human plasma (Octaplas), and/or platelets units at*
23
24 *hospital discharge*: This refers to the transfusion of these blood products from the beginning of
25
26 surgery to the day of discharge.

27
28
29 *Reintervention for bleeding*: any reoperation for postoperative bleeding, regardless of concomitant
30
31 hemodynamic problems.

32
33
34 *Reintervention for hemodynamic problems*: any reoperation for hemodynamic instability. This can
35
36 also be associated with excessive bleeding: in this case, both categories (“Reintervention for
37
38 bleeding” and “Reintervention for hemodynamic problems”) will be marked.

39
40
41 *Pericardial effusion requiring treatment*: any pericardial effusion requiring interventional treatment
42
43 (e.g. pericardiocentesis, subxifoid drainage, resternotomy, etc) due to cardiac tamponade, sub-
44
45 tamponade, or hemodynamic instability refractory to conservative treatment-strategies.

46
47
48 *Acute renal failure*: severity of acute renal failure after surgery will be graded in AKIN stages from
49
50 1 to 3, according to VARC-2 criteria (36).

51
52
53 *Highest postoperative creatinine level*: the highest level of serum creatinine detected after surgery
54
55 during the in-hospital stay. Creatinine levels will be reported in $\mu\text{mol/L}$

Renal replacement therapy: the need for renal replacement therapy will be dichotomized into “temporary” or “permanent” (the latter in the event of death while on renal replacement therapy, or if discharged on renal replacement therapy, or in case of life-long need). Type of renal replacement therapy (e.g. dialysis, CVVH, SCUF, etc.) will be also collected as a note.

Gastrointestinal complications: any gastrointestinal complication requiring endoscopy and/or surgical treatment. Endoscopic diagnostic procedures without any associated interventional procedure (diagnostic only) will not fit this definition.

Post-operative infection: classified as: 1) surgical site infection; 2) organ infection (respiratory, urinary, gastrointestinal infection); 3) systemic infection (sepsis) 4) index valve/device infection. Wound complications are graded according to the Centre for Disease Control and Prevention definitions of surgical site infections (49). Any surgical site infection occurring within three months after surgery will be considered as a postoperative wound infection.

Early repeated intervention for index intervention failure: This refers to any surgical or percutaneous procedure on the aortic valve and/or the coronary arteries, performed during the same hospital stay for any prosthesis-related or graft-related complication. These events will be marked as occurring or not, and further detailed in their nature (“valvular early procedure”, “coronary early procedure” or “coronary + valvular early procedure”). Further details will be collected as explanatory notes.

Length of stay in the intensive care unit: number of days spent in the intensive care unit from surgery. Readmissions to intensive care unit will be considered and included in the number. estimation.

Length of in-hospital stay: number of days spent into hospital (ICU-stay will be added) from the day of surgery to hospital discharge to any other hospital ward, rehabilitation unit or home.

Drug antithrombotic treatment at discharge: collected dichotomic (yes/no) for each of the following drugs: 1) vitamin-K antagonists; 2) new oral anticoagulants; 3) antiplatelets. Further details on type and dose of each drug will be added as a note.

Type of discharge: discharge will be categorized according to the Italian NIH classification, as follows: 1) death; 2) discharged home; 3) discharged to rehabilitation clinic; 4) voluntary discharge; 5) transferred to other hospital for acute complications; 6) transferred to other hospital for other reasons; 7) transferred to rehab/other hospital for chronic complications; 8) ordinary discharge + nurse assistance at home; 9) dismissal.

NYHA at follow-up: NYHA class will be assessed at hospital discharge, at 6 months, 1 year, and yearly, up to a 5-year follow-up.

Date of events: during follow-up, the date of each possible event will be collected as “dd/mm/yyyy”

Follow-up death: death occurring after hospital-discharge. Further dichotomization into cardiovascular and all-cause mortality is based on VARC-2 criteria (36).

Follow-up stroke: any focal or global neurological syndrome occurring after discharge and caused by ischemia and/or haemorrhage not resolving within 24 hours. The diagnosis and nature of stroke will be made on the basis of findings from brain CT, or MRI, or based on the medical report of a consultant neurologist.

Follow-up myocardial infarction: any myocardial infarction occurring after discharge and requiring medical, interventional or surgical treatment occurring after discharge.

Follow-up re-intervention on the aortic valve: re-intervention is defined as any surgical or percutaneous interventional treatment that replaces (or repairs) an aortic prosthesis implanted at the time of the index procedure which is dysfunctional for either structural or non-structural reasons.

Follow-up aortic valve-related adverse event: this includes: 1) embolism; 2) valve thrombosis; 3) bleeding events; 3) structural valve deterioration; 4) paravalvular leakage; 5) operated valve endocarditis; 6) haemolysis, based on the definitions of current Guidelines for reporting mortality and morbidity after cardiac valve interventions (37).

Follow-up repeated revascularization: any CABG and/or PCI performed after discharge for coronary graft dysfunction and/or valve-related coronary complication. Any revascularization due

to the progression of an untreated subcritical (at the time of the index procedure) coronary target will not be considered.

Need for implantable cardioverter-defibrillator: collected as a dichotomous variable (yes/no)

Composite outcome: according to VARC-2 definitions (36), this includes: 1) device success; 2) early safety at 30 days; 3) clinical efficacy after 30 days; 4) time-related valve safety

Follow-up MACCE: defined as a composite end-point including any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, follow-up repeated revascularization

Assessment of post procedural aortic prostheses performance: data on valve and prosthetic performances will be recorded according to medical reports from a consultant echocardiographer. Data will be collected before surgery, before hospital discharge, at 30 days after surgery, 6 months, 1 year after implantation, and yearly thereafter up to 5 years of follow-up. Data collected at echocardiographic examination are based on VARC-2 criteria (36), and aimed at exploring prosthetic valve-performance and ventricular performance. A minimum set of echocardiographic data will be considered, as follows: 1) left ventricular (LV) function (EF% based on Simpson’s method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade (defined as mild, moderate or severe based on several different echocardiographic indexes as regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local institutional policies). Further assessment of “intra-prosthetic”, “peri-prosthetic” or “combined intra+peri-prosthetic” regurgitation will be added.

Short-Form 8 SF-8 Health Survey questionnaire: will be based on eight questionnaire items reported in Table 4 (50). This examination will be administered before surgery, at hospital discharge, at 30-days, at 6 months, at 1 year, and yearly thereafter up to 5-year follow-up.

ETHICS AND DISSEMINATION

The study will be approved by the local Institutional Review Boards/Ethical Committees, according to local or national guidelines for approval of registry studies. Patient's informed consent will be always obtained.

Research findings based on data from the E-AVR registry will be disseminated among the scientific community. They will be presented at international congresses and published in peer reviewed international journals in the fields of cardiac surgery and cardiology. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship. Data collection, analysis and writing process will be monitored by the Steering Committee of the E-AVR, which is made up of the Principal Investigator and a Representing Member from each of the participating centres. A complete list of the E-AVR Collaborators is reported in Appendix. The Members of the Steering Committee will take responsibility for the quality of data through local audit. The Steering Committee will evaluate any study proposal and accept/reject it by vote after review and discussion of its feasibility.

Investigators will be eligible for authorship if they contribute substantially to study planning, data collection, data analysis and interpretation, writing and critical review of the manuscripts. Two authors per centre will be included as main authors of each study. As a member of the Steering Committee, the Representing Member will take any decisions on co-authorship related to his/her centre on the basis of the above criteria. Those researchers who plan a sub-study, perform the analysis and write the article will be the first and last authors of the study. The Principal Investigator will finalize the database and will guarantee that each Steering Committee Member has a copy of the complete database. Analyses will be performed and/or monitored by an independent Central Core Statistic Laboratory. When an article is submitted to a journal with a maximum number of

1 authors, the Steering Committee will decide on the authors on the basis of their contribution to the
2
3 design of the study, data collection, analysis, interpretation of data, writing, and critical review of
4
5 the paper. In the event of future merging with other contemporary registries (e.g. collecting data on
6
7 concurrent interventional – i.e. transfemoral or percutaneous trans-axillary - TAVR procedures), the
8
9 co-authorship of comparative studies (e.g. between surgical and interventional treatments) will be
10
11 defined by the Steering Committees of the different registries involved.
12
13
14

15 *Conclusions*

16
17 This multicenter, prospective open registry has been designed with the aim of investigating a
18
19 number of controversial issues regarding current treatment-options and risk factors for the surgical
20
21 therapy of SAVS with or without CAD. Several studies and information are expected to derive from
22
23 the data collected in the registry. These data will provide further knowledge on the mechanisms
24
25 leading to adverse events during or after surgery for SAVS and help their prevention, thus allowing
26
27 a “tailored” surgical approach for the treatment of this disease.
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47
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49
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52 **COMPETING INTEREST STATEMENT**

53
54 None to declare.
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FIGURE LEGENDS

Figure 1. Flowchart of enrolment criteria and surgical techniques considered in the registry

Figure 2. Flowchart of time-points for data collection

For peer review only

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AUTHOR'S CONTRIBUTIONS:

F. Onorati: Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

R. Gherli: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

G. Mariscalco: Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

E. Girdauskas: Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

E.O. Quintana: Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

F. Santini: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

M. De Feo: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

S. Sponga: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

P. Tozzi: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

M. Bashir: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

V. Anttila: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

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A. Perrotti: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

A. Pappalardo: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

F. Biancari: Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

V.G. Ruggieri: Conception of the study, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

M. Rinaldi: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

C. Antona: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

F. Nicolini: Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing

Appendix. E-AVR Collaborators

1. **Tiziano Gherli, MD** – Cardiac Surgery Unit, University of Parma, Parma, Italy
2. **Giuseppe Faggian, MD** and **Livio San Biagio, MD** – Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy
3. **Francesco Musumeci, MD** – Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy
4. **Hermann Reichenspurner, MD** – Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany
5. **Manuel Castellà, MD** – University Hospital Clinic, Barcellona, Spain
6. **Antonio Salsano, MD** – Cardiac Surgery Unit, University of Genova, Genoa, Italy
7. **Alessandro Della Corte, MD PhD** and **Ciro Bancone, MD** - Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy
8. **Ugolino Livi, MD** - Cardiothoracic Department, University Hospital of Udine, Udine, Italy
9. **Nicola Masala, MD** and **Gavin J. Murphy, MD** - Department of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK
10. **Sidney Chocron, MD PhD** - Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France
11. **Giuseppe Gatti, MD** and **Luca Maschietto, MD** - Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy
12. **Stefano Salizzoni, MD** – Dpt of Cardiac Surgery, Torino University Hospitals, Turin, Italy

TABLE 1: Stages of renal failure.

Stages	eGFR level (mL/min/1.73 m2)
1	90 or above
2	89 to 60
3a	59 to 44
3b	44 to 30
4	29 to 15
5	Less than 15 or on dialysis

TABLE 2: New York Heart Association functional classes.

<i>Class</i>	<i>Definition</i>
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest
IV	Severe limitations. Experiences symptoms even while <i>at rest</i> . Mostly bedbound patients

TABLE 3: Definition criteria of type V myocardial infarction.

Baseline condition	Definition
1. In patients with normal baseline CK-MB or cTn (I or T)	The peak CK-MB measured within 48 hours of the procedure rises to $\geq 10 \times$ the local laboratory upper limit of normal (ULN), or to $\geq 5 \times$ ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the procedure rises to $\geq 70 \times$ the local laboratory ULN, or $\geq 35 \times$ ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB.
2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Table 4: SF-8TM Health Survey

Date _____ Name _____

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. For each of the following questions, please mark an [x] in the one box that best describes your answer.

1) Overall, how would you rate your health during the past 4 weeks?

Excellent Very Good Good Fair Poor Very Poor

2) During the past 4 weeks, how much did physical health problems limit your physical activities (such as walking or climbing stairs)?

Not at all Very little Somewhat Quite a lot Could not do physical activities

3) During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?

Not at all Very little Somewhat Quite a lot Could not do daily work

4) How much bodily pain have you had during the past 4 weeks?

None Very mild Mild Moderate Severe Very severe

5) During the past 4 weeks, how much energy did you have?

Very much Quite a lot Some A little None

6) During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?

Not at all Very little Somewhat Quite a lot Could not do social activities

7) During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?

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Not at all	Slightly	Moderately	Quite a lot	Extremely
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8) During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

Not at all	Very little	Somewhat	Quite a lot	Could not do daily activities
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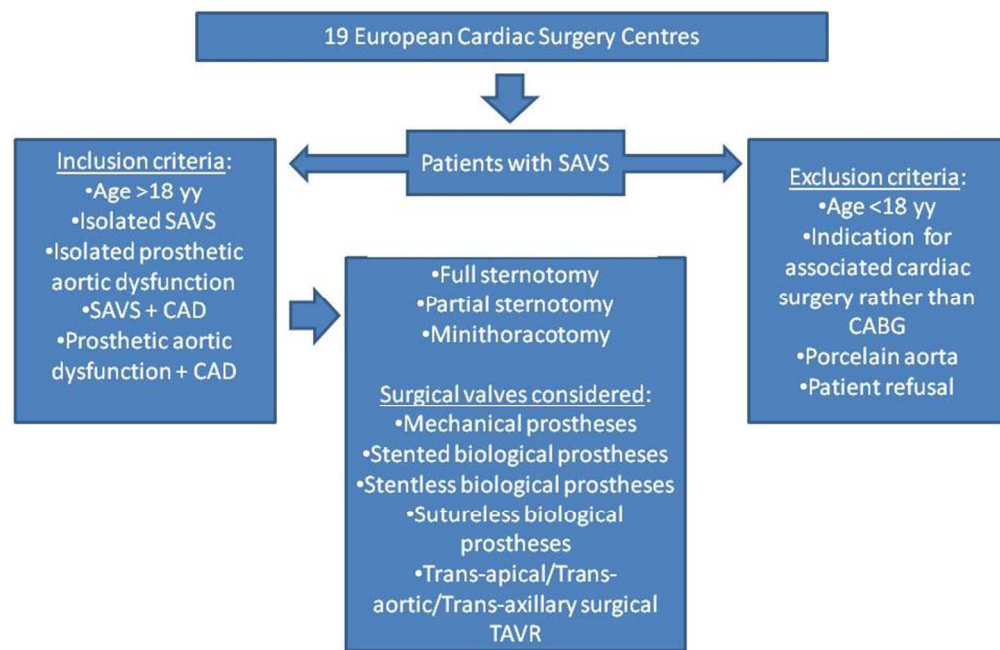


Figure 1. Flowchart of enrolment criteria and surgical techniques considered in the registry

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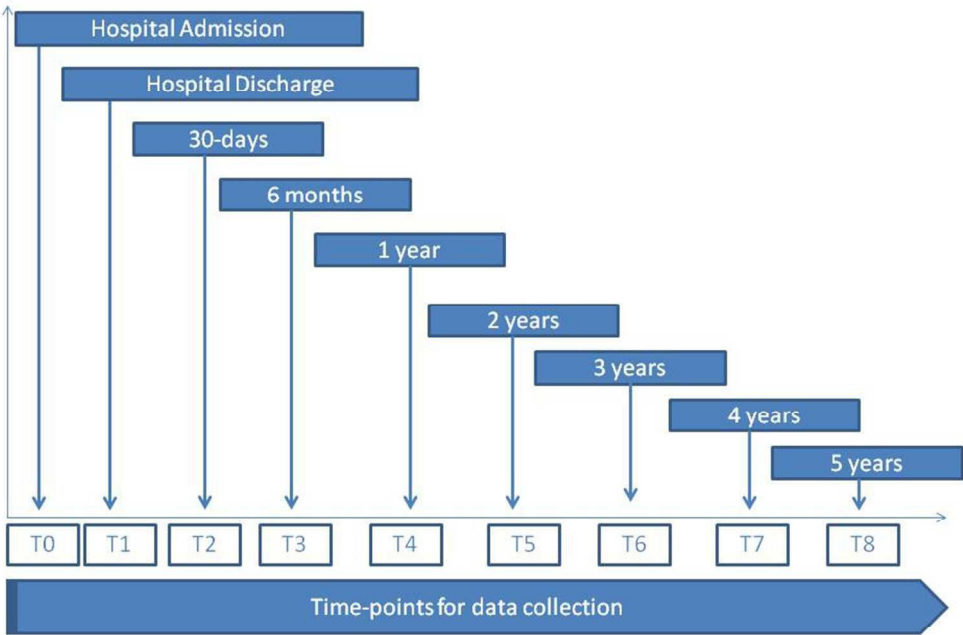


Figure 2. Flowchart of time-points for data collection

254x190mm (96 x 96 DPI)

BMJ Open

Outcomes comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)

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Manuscripts

Outcomes comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)

F. Onorati¹, R. Gherli², G. Mariscalco³, E. Girdauskas⁴, E.O. Quintana⁵, F. Santini⁶, M. De Feo⁷, S. Sponga⁸, P. Tozzi⁹, M. Bashir¹⁰, A. Perrotti¹¹, A. Pappalardo¹², V.G. Ruggieri¹³, G. Santarpino¹⁴, M. Rinaldi¹⁵, C. Antona¹⁶, F. Nicolini¹⁷, on behalf of E-AVR Collaborators.

¹Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; ²Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy; ³Department of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK; ⁴Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany; ⁵University Hospital Clinic, Barcellona, Spain; ⁶Cardiac Surgery Unit, University of Genova, Genoa, Italy; ⁷Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy; ⁸Cardiothoracic Department, University Hospital of Udine, Udine, Italy; ⁹Cardiac Surgery Unit, Centre Hospitalier Universitaire Vaudois, Lausanne; ¹⁰Division of Cardiac Surgery, St. Barth Hospital NHS, London, UK; ¹¹Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France; ¹²Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy; ¹³Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN, Hopital Robert Debre', Reims, France; ¹⁴Cardiovascular Center, Klinikum Nürnberg – Paracelsus Medical University, Nuremberg, Germany; ¹⁵Department of Cardiac Surgery, Torino University Hospitals, Turin, Italy; ¹⁶Department of Cardiac Surgery, Ospedale Sacco, Milan, Italy; ¹⁷Div. Cardiac Surgery, University of Parma, Parma, Italy

Corresponding Author: Francesco Onorati, MD PhD – Div. Cardiac Surgery, Dpt. of Surgery, University of Verona Medical School - Piazzale Stefani n.1 – 37126 – Verona, Italy. Phone: 0039 (0)45 8121945; Fax: 0039 (0)45 8123308; Email: francesco.onorati@aovr.veneto.it

ABSTRACT

Introduction: Traditional and transcatheter surgical treatments of severe aortic valve stenosis (SAVS) are increasing in parallel with the improved life-expectancy. Recent randomized trials (RCTs) reported comparable or non-inferior mortality with transcatheter treatments compared to traditional surgery. However, RCTs have the limitation of being a mirror of the predefined inclusion/exclusion criteria, without reflecting the “real clinical world”.

Technological improvements have recently allowed the development of minimally invasive surgical accesses and the use of sutureless valves, but their impact on the clinical scenario is difficult to assess because of the monocentric design of published studies and limited sample-size. A prospective multicentre registry including all patients referred for a surgical treatment of SAVS (traditional, through full-sternotomy; minimally-invasive; or transcatheter; with both “sutured” and “sutureless” valves) will provide a “real-world” picture of available results of current surgical options, and will help to clarify the “grey zones” of current guidelines.

Methods and analysis: E-AVR is a prospective observational open registry designed to collect all data from patients admitted for SAVS, with or without coronary artery disease, in 17 cardiac surgery Centres located in six countries (France, Germany, Italy, Spain, Switzerland, and United Kingdom). Patients will be enrolled over a 2-year period and followed-up for a minimum of 5 years to a maximum of 10 years after enrolment. Outcome definitions are concordant with VARC-2 criteria and established guidelines. Primary outcome is 5-year all-cause mortality. Secondary outcomes aim at establishing “early” 30-day all-cause and cardiovascular mortality, as well as major morbidity, and “late” cardio-vascular mortality, major morbidity, structural and non-structural valve complications, quality of life and echocardiographic results.

Ethics and dissemination: The study protocol is approved by Local Ethics Committees. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship.

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STRENGTHS AND LIMITATIONS OF THIS STUDY:

- The protocol addresses the important question of which surgical treatment offers the most benefits in the management of patients with severe aortic valve stenosis, with or without concomitant coronary artery disease.
- The expected large sample size will guide sub-analyses aimed at identify specific patient characteristics and different risk-profiles, which are better served with alternative surgical techniques.
- The minimum 5-year and maximum 10-year follow-up will provide answers about the mid-to-long term safety and efficacy of recent surgical innovations (i.e. sutureless valves, minimally invasive approaches, surgical TAVR), whose follow-up data are still lacking in current literature
- The present multicentre registry has clearly established aim, inclusion and exclusion criteria, short-term and follow-up primary and secondary endpoints, as well as state-of-the-art methods for data collection and endpoints definition
- Limitations include absence of a Central Core Laboratory for echocardiographic assessment, variations in postoperative and follow-up management, which are based on local Institutional policies, and lack of blinding between the central statistical core-lab performing the analyses and the employed surgical techniques
- The absence of any external sponsor certainly limits research resource allocation, but also guarantees the certainty for the absence of any bias or conflict of interest related to the investigated topics

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3 **INTRODUCTION**

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5 The prevalence of severe aortic valve stenosis (SAVS) correlates with age, and its treatment is

6 expected to increase parallel to the improved life-expectancy reported in Western Countries (1-2).

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9 Traditional surgical aortic valve replacement (SAVR) has been the gold standard of treatment for

10 decades, with well-documented benefits in terms of symptom improvement and survival (3-4).

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13 Recent technological advances allowed interventional and surgical transcatheter aortic valve

14 replacements (TAVR), which proved to be effective alternatives to traditional SAVR, in both high-

15 risk and intermediate-risk patients (5-12). Therefore, SAVR and TAVR represent nowadays the

16 standard surgical armamentarium for aortic valve replacement.

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22 Alternative surgical approaches, based on the concept of TAVR (13,14), have in fact been

23 developed. There are on the market two types of “sutureless” valves (i.e. Sorin Perceval and

24 Edwards Intuity) at the moment - aimed at reducing some surgical drawbacks such as cross-clamp

25 time and myocardial ischemia-reperfusion injury (13,15-20) – and it is possible that new

26 “sutureless” valves will enter the market in the next future. Moreover, different mini-thoracotomy

27 and mini-sternotomy approaches to SAVR have been widely adopted by the surgical community -

28 with both “sutured” and “sutureless” valves - in order to reduce surgical trauma, systemic

29 inflammatory response, and major organ morbidity (13,15,16). Various different combinations of

30 minimally invasive accesses and the use of last-generation valves have been reported to date

31 (14,17,18). But despite early enthusiasm about preliminary results with these technological

32 improvements, none of these techniques has yet replaced traditional SAVR in standard surgical

33 practice, mainly because reporting of results of these alternative techniques tends to be biased by

34 single-centre design, limited sample-size, and the strict inclusion/exclusion criteria of the published

35 studies (13,14).

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52 Another “hot topic” in this debate relates to valve durability, given that the long-term durability of

53 both TAVR and sutureless valves is as yet unknown. Indeed, standard “sutured” surgical valves

54 demonstrated excellent durability, both in the very-long term and in very-young adults below the

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65-year cut-off age (21-23), which is still the threshold for biological valves recommended by European Society of Cardiology (ESC) / European Association for CardioThoracic Surgery (EACTS) guidelines (24). This issue is of particular interest, given that the use of TAVR has increased in younger intermediate-risk patients, despite recent caveats relating to early degeneration of TAVR (25,26).

Similarly, improved life-expectancy has led to a growing number of patients with degenerated dysfunctioning aortic bioprostheses requiring surgical treatment. Again, surgical aortic prosthetic replacement (SAPR) has been traditionally considered the only treatment strategy for these patients, given the excellent results, recently confirmed by several studies (27,28). Again, transcatheter treatments ("valve-in-valve") have recently demonstrated comparable or sometimes superior results in redo-scenarios (29). Therefore, data on the efficacy, safety and durability of these technological improvements are essential for providing "strong" statements in future guidelines, and for evaluating the extension of these techniques to low-risk and young patients in the future.

Finally, it is well known that critical coronary artery disease (CAD) often coexists with SAVS. Although the standard treatment option for these patients has traditionally been SAVR plus coronary artery bypass grafting (CABG), the introduction of TAVR and minimally invasive surgical alternatives has considerably changed the available options, paving the way to combined less-invasive SAVR+CABG and/or TAVR±PCI (either before, during or after the surgical procedure) (30-34). Again, there is a great deal of confusion on the topic, and there are unanswered questions on the efficacy and safety of these options, as well as on what to expect from late follow-up when compared to the standard practice of SAVR+CABG.

Robust early and follow-up data on the safety and efficacy of surgical TAVR, last-generation sutureless surgical valves, and minimally-invasive approaches compared with standard SAVR, with or without a contemporary (surgical or interventional) treatment of concurrent CAD, are still lacking for a real-world large population of patients at variable surgical risk. Such data is urgently required for the correct allocation of therapy in daily surgical practice. Furthermore, data on quality

of life and functional echocardiographic results with different surgical alternatives might similarly help physicians in decision-making in local “Heart Teams”. Data from a multicentre, real-world, open registry enrolling all patients with SAVS±CAD consecutively referred to several Centres at different European latitudes should help to answer some of these open questions. Here, we describe the rationale and the study protocol of the European Aortic Valve Registry (E-AVR), a multicenter prospective observational open registry on aortic valve surgical practice.

METHODS AND ANALYSIS

Rationale of the study and aim

Improvements in surgical treatment of cardiac diseases can be obtained with the implementation of current techniques and the development of new methods, based on information from large clinical datasets (35). The main strength of a prospective clinical open registry is the high external validity, given that data are collected in the settings of standard clinical practice. Moreover, large sample size enables a better estimation of event rates, and allows the investigation of hard endpoints and outcomes, by means of a wide population of patients from different institutions and with extremely limited exclusion criteria.

Importantly, clinical registries may provide data on long-term outcomes occurring after the study period of a trial (35). They are more practical than randomized controlled trials, require fewer resources, and have less stringent inclusion and exclusion criteria for patient enrolment. Finally, clinical findings from registries have even more significance when patient-populations derive from different geographic areas, with heterogeneous referral pathways, baseline clinical characteristics, and perioperative treatment strategies. All these features substantiate the concept of “a real world practice” underlying any “registry-study”.

Therefore, the rationale of this European multicenter observational open registry is to prospectively collect data on baseline characteristics, treatment options, perioperative management and postoperative outcome of all patients consecutively undergoing surgical treatment of SAVS

(regardless of gradients, AVA or AVAi)±CAD or aortic prosthetic dysfunction±CAD at 17 European university or non-university tertiary hospitals located in six European countries (France, Germany, Italy, Spain, Switzerland, and United Kingdom). The complete list of E-AVR Collaborators is reported in the Appendix.

The primary aim of the study is a 5-year comparison between SAVR and surgical TAVR: we hypothesize to report a 10% superiority in terms of all-cause mortality in favor of SAVR vs TAVR. For the purpose of this study, patients will be consecutively enrolled for a 2-year period, and will be followed-up for a minimum of 5 years after the index surgical treatment. Maximum follow-up length will be 10 years after surgery.

The following surgical options will be considered:

- 1) SAVR with mechanical valves
- 2) SAVR with biological valves (either sutured or sutureless, stented or stentless)
- 3) Surgical TAVR (either transapical, trans-axillary, or transaortic)

Similarly, the following surgical approaches will be considered:

- 1) Full sternotomy
- 2) Mini-thoracotomy (either left-sided for TAVR or right-sided for SAVR)
- 3) Partial-sternotomy

Patient allocation to a specific surgical procedure will be based on the local Heart Team decision at each Institution, according to standard clinical practice and current guidelines (2).

A flow-chart of the enrolment criteria and of the surgical techniques considered in the registry is provided in Figure 1.

Criteria for registry-enrolment

The following inclusion and exclusion criteria will be considered:

Inclusion criteria

- Age >18 yy
- Isolated SAVS with or without concomitant aortic valve regurgitation

- Isolated prosthetic aortic dysfunction
- SAVS + coronary artery disease (CAD)
- Prosthetic aortic dysfunction + CAD
- Elective, urgent and emergent procedures
- Endocarditic aetiology

Exclusion criteria

- Patients undergoing concomitant mitral valve surgery, or tricuspid valve surgery, or aortic surgery (i.e. composite aortic valve and ascending aorta replacement with or without circulatory arrest), or atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG)
- Concomitant aortic root procedure (i.e. Bentall operation, David operation, homografts, autografts)
- SAVR with techniques of aortic annular enlargement
- Porcelain aorta
- Pure aortic valve regurgitation
- Percutaneous TAVR requiring surgical cut-down (i.e. failure to comply with a full percutaneous approach, thus configuring a “hybrid procedure”)
- Patient refusal

Patients will be recruited in a consecutive series from each institution, and their data collected in a dedicated on-line datasheet. The recruitment period will be 24 months, from 1st October 2017 to 30th September 2019. Every patient will be followed up at 30 days, 6 months, 1 year, and yearly thereafter, up to a minimum of 5 years after the index surgical procedure (Figure 2). Afterwards yearly follow-up will be closed at the completion of the 10th year from surgery for each patient. On the basis of historical cohort data of local institutions, we expect to enrol a minimum of 4000 patients at the end of the first year, and a minimum of 8000 patients at the end of the second year of enrolment.

Informed consent

Written informed consent will be obtained from the patient or patient's authorized representative prior to enrolment in the Registry. In case of emergent surgery, informed consent will be collected from the patient's family (or legal representative) before surgery, as well as from the patient after surgery (if unable to give it before intervention). This consent will be waived in case of death or severe neurological damage precluding adequate postoperative patient informed consent. The study will be conducted in accordance with the provisions of the Declaration of Helsinki. The study is registered in Clinicaltrials.gov. (No. NCT03143361)

Data management and monitoring

Data will be collected into a dedicated datasheet with predefined variables. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Centre (2 letters), the initial of name (1 letter) and surname (1 letter), and the date of birth (dd.mm.yyyy) (e.g. Mr. John Smith, born on February 18th, 1953; enrolled in London = LOJS18021953). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity.

All data will be retained in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.

Baseline characteristics, operative details and outcome data pertaining hospitalization will be prospectively collected from hospital registries. Variables and events occurring after the index hospital discharge will be collected from outpatient clinics at the individual Institutions, and linking with regional Social Security Death and Events Master files where available. In case of

absent/missing data, variables and events will be collected by direct phone contact with general practitioners, and only if persistently missed by phone contact with patients and families.

Events and outcome variables will be adjudicated after agreement of two local E-AVR Investigators, and collected at local Institutions. In the event of controversy on outcome adjudication between the two local E-AVR Investigators, the outcome will be discussed and adjudicated after a final consult inside the E-AVR Steering Committee.

Storage, analysis and auditing of data will be accomplished by an independent Central Core Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy). Auditing of the dataset will be performed every six months by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator and E-AVR Steering Committee for further data checking and merging. Incomplete or contradictory data with patient identification code will be sent from Central Core Statistical Lab to the E-AVR Steering Committee local member for further data checking, review, correction and merging. The entire set of statistical analyses will be available to all E-AVR researchers for the interpretation of data.

Statistical methods

An independent central statistical Core Lab will perform all the statistical analyses derived from this registry.

Given the PARTNER TRIAL 5-year all-cause mortality risk (67.8% after TAVR and 62.4% after SAVR) – accepting a type 1 error of 5% - the overall number of patients needed to achieve 80% power (1-beta) for a mortality odds of 1.1 (10% mortality difference) is 2866 patients (i.e. 1433 patient/group) (7). Therefore, the expected number of 8000 patients is far beyond the requested sample size of the primary objective of the trial, and further accounts for risk-adjustment methodologies and the expected 1.5% (historical data) of lost to follow-up.

Continuous variables will be reported as mean and standard deviation or median and interquartile range, as appropriate. Dichotomous and nominal variables will be reported as counts and

percentages. Univariate analysis will be performed using the Mann-Whitney U test and Student's t-test for continuous variables (pending the not-normal or normal distribution respectively), the Kruskal-Wallis test (independent multilevel ordinal variables), Wilcoxon test (for paired variables), Fisher exact test and Chi-square test (for dichotomous/nominal variables) and Kaplan-Meier test (for time-dependent dichotomous variables). Multivariable analyses will be performed using logistic regression method (for categorical dependent variable), classification tree analysis (for target variables with a discrete set of value), linear regression (for continuous dependent variable) and ordinal regression methods (for ordinal dependent variable), as well as Cox-proportional hazards method (to test the effects of covariates on time-dependent dichotomous variables). Significant differences between study groups will be adjusted by using propensity score as covariate or by one-to-one propensity score matching. Matching will be performed using a caliper width of 0.2 of the standard deviation of logit of the propensity score. Multiple propensity score adjusted analysis will be performed in case of multiple study groups. A Bayesian hierarchical approach will be used in the case of significant variability between centres. Missing values will be replaced and estimated using multiple imputations. Furthermore, sensitivity analysis will be executed using complete-case analysis. Interim analyses are planned at different time-points (see Ethics and Dissemination). Critical p-values of accomplished interim analyses will be corrected according to the Armitage-McPherson adjustment (36).

Early and late endpoints

Outcome endpoints will be defined according to current guidelines, i.e. VARC-2 definitions (37) and Guidelines for reporting mortality and morbidity after cardiac valve interventions (38).

In more detail, the following outcome variables will be collected:

Primary outcome of the E-AVR registry: 5-year all-cause mortality

Secondary outcomes of the E-AVR registry: these will be dichotomized into “early” at 30-day (i.e. during hospitalization, at home if discharged, or during “rehab-hospitalization” at any time point if never discharged home) and “late” (after the patient is discharged home):

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3 1) Early secondary outcomes: all-cause mortality, cardiovascular mortality, stroke, acute
4 myocardial infarction (AMI) (39) , postoperative need for prolonged use of inotropes (>72
5 hours), postoperative need for intra-aortic balloon pump (IABP) or extracorporeal
6 mechanical oxygenation (ECMO), surgical site infection, blood losses and use of blood
7 products (during hospitalization for the index surgical procedure), nadir hematocrit, nadir
8 hemoglobin, resternotomy for bleeding, atrial fibrillation (first event and number of events),
9 cardiac conduction disturbances, need for new permanent pace-maker implantation, acute
10 kidney injury (following AKIN classification), pericardial effusion requiring treatment,
11 length of stay in the intensive care unit, length of in-hospital stay (for the index procedure),
12 device success, early safety, clinical efficacy, time-related valve safety, echocardiographic
13 data of prosthesis performance, early repeat surgery for failure of the index procedure (any
14 “redo” before discharge home or to rehabilitation clinic).
15
16 2) Late secondary outcomes (collected starting from discharge to the end of the 10th year after
17 the index procedure): cardiovascular mortality, all-cause mortality (from 1 to 4 years after
18 surgery, then from 6 to 10 years), stroke, acute myocardial infarction, reintervention on the
19 aortic prosthesis, repeat revascularization (either with percutaneous coronary intervention or
20 CABG), prosthetic thrombosis, embolism, bleeding events, structural valve deterioration,
21 paravalvular leakage, prosthetic endocarditis, need for permanent pacemaker, need for
22 implantable cardioverter-defibrillator, MACCE (defined as a composite end-point including
23 any of the following adverse events: death from cardiovascular cause, stroke, myocardial
24 infarction, repeated revascularization), time-related valve safety, quality of life (QoL; defined
25 according to Short Form-8 questionnaire; QoL will be assessed during follow-up visits at
26 outpatient clinics or, if other methods are not possible, by telephone interview);
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28 echocardiographic data of prosthesis performance.
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54 Echocardiographic data of prosthesis performance are defined according to the Valve Academic
55 Research Consortium-2 definitions (37). Although the absence of a Central Core Echocardiographic
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Laboratory might represent a limitation, all echocardiographic data will be collected from 3rd level nationally and/or internationally certified Institutional Echo Laboratories. Collection of data is under the responsibility of the Steering Committee local member at each participating Centre. Data will be audited from the Central Core Laboratory on a regular basis, as reported previously. Outcomes and their definition criteria are described in detail in the following section of this article.

Data collection

Participating Centre: Each participating Centre will be anonymized by identification with a capital letter. The correspondence between Centres and capital letters will only be known by the PI of the study. The Central Core Laboratory analyzing the data will be blinded towards the surgical teams.

Units of measurement: Laboratory data will be collected according to fixed units of measurement in order to avoid any problem stemming from differences in units used by the various participating centres, during data merging and analysis. The fixed units of measurement are reported in the dedicated CRF datasheet.

Laboratory parameters: baseline levels of haemoglobin, haematocrit, platelets, blood glucose, HbA1c, C-reactive protein, TT-INR and albumin will be collected.

Hypertension: arterial blood pressure > 140/90 mmHg or anti-hypertensive treatment.

Diabetes: diabetes mellitus requiring diet, oral or insulin treatment.

Preoperative creatinine levels: this parameter is obtained on the day before surgery and is expressed in $\mu\text{mol/L}$.

Chronic Kidney Disease: the severity of renal failure will be classified as shown in Table 1. It is stratified by the estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease Study Group modified formula (40). eGFR for calculation of the

EuroSCORE II (41) will be estimated using the Cockcroft-Gault formula (42) according to the criteria of this risk scoring method.

Dialysis: peritoneal or hemo-dialysis before surgery.

Chronic obstructive pulmonary disease (COPD): any long-term use of bronchodilators or steroids for lung disease.

Oxygen therapy: long-term oxygen therapy for respiratory failure.

Liver disease: different degrees of liver failure stratified according to the Child-Pugh classification (43).

Active neoplasia: any active malignancy.

Preoperative stroke: any preoperative focal or global neurological syndrome caused by ischemia or haemorrhage not resolving within 24 hours.

Neurological dysfunction: disabling outcomes in ambulation and / or normal motor functions, according to EuroSCORE II definition (41).

Extracardiac arteriopathy: one or more of the following: claudication, carotid occlusion or >50% stenosis, amputation for arterial disease, previous or planned intervention on the abdominal aorta, limb arteries or carotids.

Preoperative ECG: sinus rhythm, or atrial fibrillation; or first degree AV block; or right bundle block; or left bundle block; or pacemaker rhythm.

Preoperative myocardial infarction: any preoperative myocardial infarction.

Previous vascular surgery: history of surgical or endovascular procedure of the thoracic or abdominal aorta and/or the iliac-femoral arteries.

Previous cardiac surgery: one or more previous cardiac operations requiring opening of the pericardium.

Type of previous cardiac surgery: description of previous cardiac operation.

Previous aortic valve replacement: description of prosthesis and date of operation.

Previous percutaneous coronary intervention: any previous percutaneous coronary intervention.

Etiology of aortic valve disease: native valve disease (degenerative; rheumatic; endocarditic) or prosthetic valve disease.

Endocarditis: any diagnosis of valve endocarditis made by the Heart Team and/or antibiotic treatment for endocarditis at the time of surgery. Subclassification into acute, subacute, and healed endocarditis based on Current Guidelines will be added (44).

Endocarditis etiology: microbe isolated for the diagnosis of endocarditis

NYHA functional classes: defined according to the criteria listed in Table 2 (45).

Aortic valve stenosis: severity of aortic valve stenosis before surgery will be graded as moderate or severe according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (46).

Aortic valve regurgitation: Severity of aortic valve regurgitation before surgery will be graded in classes from 0 to 3, and the grade of severity will be evaluated according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (46).

Associated critical coronary artery disease: presence of stenosis of at least 70% in any major epicardial coronary artery. Number of main vessels involved will be recorded. Patients with stenosis of the left main coronary artery will be considered as having at least two-vessel disease.

Associated left main coronary artery disease: Any LMSD > 50%

Mitral valve regurgitation: severity of concurrent mitral valve regurgitation - though not requiring surgery - will be graded in classes according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (46).

Left ventricular function: last measured left ventricular ejection fraction before surgery (in any case before induction of anesthesia).

Pulmonary hypertension: absent: <31 mmHg; moderate: 31-55 mmHg; severe: >55 mmHg, according to EuroSCORE II definition (41). Systolic pulmonary pressure will be estimated at echocardiography, at least before induction of anesthesia.

Preoperative echocardiography data: aortic valve area, peak transvalvular gradient, mean transvalvular gradient, aortic annulus diameter, maximum jet velocity (TTE) will be recorded.

Preoperative multislice CT scan data: annulus circumference; valvular area; calcium score (collected for all surgical TAVR, and only if available for other surgical techniques)

Diseased ascending aorta: any sign of diffuse atherosclerosis in the ascending aorta at palpation or epiaortic ultrasound (porcelain aorta is not considered).

Montgomery classification: if available, echocardiographic Montgomery classification of aortic atheromas will be provided.

Preoperative antithrombotic or antibiotic drug treatment: data on all antithrombotic drugs administered before surgery will be collected. The date of pause of drug treatment is the last day the patient received the drug. Data on any oral or intravenous antibiotics administered preoperatively without prophylaxis purpose, i.e. for any preoperative infectious condition, will be collected.

Elective surgery: elective procedure scheduled for stable aortic valve disease.

Urgent surgery: procedure indicated by medical factors which require the patient to stay in hospital to have operation before discharge.

Emergency surgery: procedure performed before the beginning of the working day after the decision to operate.

Frailty: Preoperative patient's frailty is graded according to Geriatric Status Scale, as proposed by Rockwood et al (47).

Critical preoperative status: ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anesthetic room, preoperative

inotropes or IABP, preoperative acute renal failure (anuria or oliguria <10ml/hr), according to EuroSCORE II definition (41).

EuroSCORE II: this risk score is calculated using the on-line calculator available at <http://www.euroscore.org/calc.html> and reported as a percentage. The risk factors included in the EuroSCORE II and collected in the E-AVR registry are defined according to the EuroSCORE II criteria (41).

STS score: this risk score is calculated using the on-line calculator available at <http://riskcalc.sts.org/stswebriskcalc/#/> and reported as a percentage. The risk factors included in the STS score and collected in the E-AVR registry are defined according to the STS score criteria (48).

Surgical chest access: classified as 1) full sternotomy; 2) minithoracotomy; 3) partial-sternotomy.

Aortic valve replacement data: classified as 1) mechanical prosthesis; 2) stented biological prosthesis; 3) stentless biological prosthesis; 4) sutureless biological prosthesis; 5) trans-apical TAVR; 6) transaortic TAVR. The description of model and diameter of the prosthesis implanted and possible need for proctored procedure will also be collected.

Other intraoperative data: type of cardioplegia and its temperature, duration of extracorporeal circulation (ECC), nadir temperature of ECC, and aortic cross-clamping time, need for re-aortic cross-clamping for any reason (paravalvular leak, coronary obstruction, annular rupture/hematoma, re-construction of CABG, etc), as well as details of TAVR implantation including sheath size, pre-implantation valvuloplasty, occurrence of valve-in-valve emergency procedure, the number of valves implanted, prosthesis migration, recapturing and re-positioning of the valve, post-procedural dilation, amount of contrast medium administered will be collected.

CABG details: Details of types of conduit and target vessel will be reported (e.g.: LIMA-LAD, RIMA-Dx, RA-MO. SV-DIAG): The following specifications for conduits will be used: LIMA: left internal mammary artery; RIMA: right internal mammary artery; RA: radial artery; GEA: gastro-epiploic artery; SV: saphenous vein. The following target acronyms will be used: DA: anterior

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3 descending; DIAG: diagonal; RX: right coronary (trunk); PDA: posterior descending; PL: postero-
4 lateral; OM: obtuse marginal. In the event of sequential grafting, the prefix "seq" will be used
5 before targets (e.g. LIMA-seq DIAG-DA)
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9 *Other CABG details:* number of distal anastomoses, completeness of revascularization.

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11 *30-day all-cause mortality:* defined as the sum of cardiovascular and non-cardiovascular, the latter
12 defined as any death in which the primary cause is clearly related to another condition not
13 contemplated by the definition "cardiovascular" (e.g. trauma, cancer, etc.), as in VARC-2 definition
14 (37), but occurring within 30-days or during index procedure hospitalization if the postoperative
15 length of stay is longer than 30 days.
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18 *30-day cardiovascular mortality:* based on VARC-2 definition (37) and occurring within 30-days or
19 during hospitalization for the index procedure if the postoperative length of stay is longer than 30
20 days. This includes: 1) death due to proximate cardiac cause (e.g. myocardial infarction, cardiac
21 tamponade, worsening heart failure, low cardiac output syndrome, etc.); 2) death caused by non-
22 coronary vascular conditions (e.g. pulmonary embolisms, stroke, aortic rupture or vascular
23 dissection, etc); 3) all procedure-related deaths (including those related to a complication of the
24 procedure or a treatment for a complication of the procedure); 4) all valve-related deaths including
25 valve dysfunction (structural or non-structural) and other valve-related adverse events; 5) sudden or
26 unwitnessed death
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42 *Type 5 myocardial infarction:* defined according to the recent criteria defined by Moussa et al. (49)
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Atrial fibrillation: any new paroxysmal/permanent atrial fibrillation episode requiring or not
requiring pharmacological or electrical cardioversion attempts. Number of recurrences will be also
collected.

Cardiac conduction disturbances: defined as a new left bundle branch block, right bundle branch
block, or AV-block (1st, 2nd or 3rd degree). Diagnosis will be based on official medical reports from a

consultant cardiologist. In case of progressive bradi-arrhythmias, the evolution of the arrhythmias will be collected.

Need for permanent PMK: collected as a dichotomic variable. Type of permanent pacing set-up (e.g. AAI, VVI, DDD, etc) will be collected.

Postoperative neurologic damage: classified as: 0) absent; 1) disabling stroke; 2) non-disabling stroke; 3) TIA, based on definitions of VARC-2 consensus (37).

Stroke classification: 1) ischemic; 2) haemorrhagic; 3) unknown, according to VARC-2 consensus (37). The diagnosis and nature of stroke will be supported by CT or MRI imaging and confirmed by a consultant neurologist.

Prolonged use of inotropes (>72 hours): This refers to the use of inotropes for >72 hours after the index operation. The type, dose and duration of administered inotropes will be also collected.

Cardiogenic shock: postoperative critical hemodynamic condition requiring mechanical ventricular-assist devices or high-dose inotropes with evidence of peripheral malperfusion. Coexistence of a cardiac index $< 1.8 \text{ l/min/m}^2$ despite adequate correction of all the coexisting preload, afterload, electrolyte and gas-analyses abnormalities will be pursued with the aid of different hemodynamic monitoring methods, according to local Institutional policies (e.g. echocardiography, Swan-Ganz catheter, PICCO, PRAM, Vigileo, etc.).

IABP: intra- or postoperative insertion of an intra-aortic balloon pump device.

ECMO: intra- or postoperative insertion of an extracorporeal mechanical pump/oxygenation device.

Bleeding: classified as 1) life-threatening or disabling bleeding; 2) major bleeding; 3) minor bleeding, according to the recent definition criteria reported by the VARC-2 document (37).

Blood loss 12 hours after surgery: the amount of postoperative blood losses from mediastinal drainages 12 hours after surgery. Intraoperative blood losses are not taken into account. Nadir haemoglobin and nadir haematocrit will be collected.

No. of transfused RBC units at hospital discharge: total amount of RBC units intra- and/or postoperatively transfused, from the beginning of surgery to the day of discharge.

No. of transfused fresh frozen plasma, pooled human plasma (Octaplas), and/or platelets units at hospital discharge: This refers to the transfusion of these blood products from the beginning of surgery to the day of discharge.

Reintervention for bleeding: any reoperation for postoperative bleeding, regardless of concomitant hemodynamic problems.

Reintervention for hemodynamic problems: any reoperation for hemodynamic instability. This can also be associated with excessive bleeding: in this case, both categories (“Reintervention for bleeding” and “Reintervention for hemodynamic problems”) will be marked.

Pericardial effusion requiring treatment: any pericardial effusion requiring interventional treatment (e.g. pericardiocentesis, subxifoid drainage, resternotomy, etc) due to cardiac tamponade, sub-tamponade, or hemodynamic instability refractory to conservative treatment-strategies.

Acute renal failure: severity of acute renal failure after surgery will be graded in AKIN stages from 1 to 3, according to VARC-2 criteria (37).

Highest postoperative creatinine level: the highest level of serum creatinine detected after surgery during the in-hospital stay. Creatinine levels will be reported in $\mu\text{mol/L}$

Renal replacement therapy: the need for renal replacement therapy will be dichotomized into “temporary” or “permanent” (the latter in the event of death while on renal replacement therapy, or if discharged on renal replacement therapy, or in case of life-long need). Type of renal replacement therapy (e.g. dialysis, CVVH, SCUF, etc.) will be also collected as a note.

Gastrointestinal complications: any gastrointestinal complication requiring endoscopy and/or surgical treatment. Endoscopic diagnostic procedures without any associated interventional procedure (diagnostic only) will not fit this definition.

Post-operative infection: classified as: 1) surgical site infection; 2) organ infection (respiratory, urinary, gastrointestinal infection); 3) systemic infection (sepsis) 4) index valve/device infection.

Wound complications are graded according to the Centre for Disease Control and Prevention

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3 definitions of surgical site infections (50). Any surgical site infection occurring within three months
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5 after surgery will be considered as a postoperative wound infection.
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7 *Early repeated intervention for index intervention failure:* This refers to any surgical or
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9 percutaneous procedure on the aortic valve and/or the coronary arteries, performed during the same
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11 hospital stay for any prosthesis-related or graft-related complication. These events will be marked
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13 as occurring or not, and further detailed in their nature (“valvular early procedure”, “coronary early
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15 procedure” or “coronary + valvular early procedure”). Further details will be collected as
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17 explanatory notes.
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20 *Length of stay in the intensive care unit:* number of hours spent in the intensive care unit from
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22 surgery. Readmissions to intensive care unit will be considered and included in the number.
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24 estimation.
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27 *Length of in-hospital stay:* number of days spent into hospital (ICU-stay will be added) from the
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29 day of surgery to hospital discharge to any other hospital ward, rehabilitation unit or home.
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31 *Drug antithrombotic treatment at discharge:* collected dichotomic (yes/no) for each of the following
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33 drugs: 1) vitamin-K antagonists; 2) new oral anticoagulants; 3) antiplatelets. Further details on type
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35 and dose of each drug will be added as a note.
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38 *Type of discharge:* discharge will be categorized according to the Italian NIH classification, as
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40 follows: 1) death; 2) discharged home; 3) discharged to rehabilitation clinic; 4) voluntary discharge;
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42 5) transferred to other hospital for acute complications; 6) transferred to other hospital for other
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44 reasons; 7) transferred to rehab/other hospital for chronic complications; 8) ordinary discharge +
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46 nurse assistance at home; 9) dismissal.
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49 *NYHA at follow-up:* NYHA class will be assessed at hospital discharge, at 6 months, 1 year,
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51 yearly up to the 5th-year follow-up, and then yearly up to follow-up closure (10 years).
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53 *Date of events:* during follow-up, the date of each possible event will be collected as “dd/mm/yyyy”
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Follow-up death: death occurring after hospital-discharge. Further dichotomization into cardiovascular and all-cause mortality is based on VARC-2 criteria (37).

Follow-up stroke: any focal or global neurological syndrome occurring after discharge and caused by ischemia and/or haemorrhage not resolving within 24 hours. The diagnosis and nature of stroke will be made on the basis of findings from brain CT, or MRI, or based on the medical report of a consultant neurologist.

Follow-up myocardial infarction: any myocardial infarction occurring after discharge and requiring medical, interventional or surgical treatment occurring after discharge.

Follow-up re-intervention on the aortic valve: re-intervention is defined as any surgical or percutaneous interventional treatment that replaces (or repairs) an aortic prosthesis implanted at the time of the index procedure which is dysfunctional for either structural or non-structural reasons.

Follow-up aortic valve-related adverse event: this includes: 1) embolism; 2) valve thrombosis; 3) bleeding events; 3) structural valve deterioration; 4) paravalvular leakage; 5) operated valve endocarditis; 6) haemolysis, based on the definitions of current Guidelines for reporting mortality and morbidity after cardiac valve interventions (38).

Follow-up repeated revascularization: any CABG and/or PCI performed after discharge for coronary graft dysfunction and/or valve-related coronary complication. Any revascularization due to the progression of an untreated subcritical (at the time of the index procedure) coronary target will not be considered.

Need for implantable cardioverter-defibrillator: collected as a dichotomous variable (yes/no)

Composite outcome: according to VARC-2 definitions (37), this includes: 1) device success (absence of procedural mortality with correct positioning of a single prosthesis and with intended performance of the prosthesis); 2) early safety at 30 days (composite endpoint of all-cause mortality, all strokes, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary obstruction requiring intervention, major vascular complication or valve-related dysfunction requiring repeat procedure); 3) clinical efficacy after 30 days (composite endpoint of all-cause

mortality, all strokes, hospitalization for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV, valve related dysfunction); 4) time-related valve safety (composite endpoint of structural valve deterioration requiring repeat procedure, prosthetic valve endocarditis, thrombosis, thrombo-embolic events or valve-related VARC bleeding).

Follow-up MACCE: defined as a composite end-point occurring after the 30-day time-point (considered as hospitalization, 30th day if discharged home, or during “rehab-hospitalization” at any time point if never discharged home), and including any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, follow-up repeated revascularization

Assessment of post procedural aortic prostheses performance: data on valve and prosthetic performances will be recorded according to medical reports from a consultant echocardiographer. Data will be collected before surgery, before hospital discharge, at 30 days after surgery, 6 months, 1 year after implantation, yearly thereafter up to the follow-up closure (10th year). Data collected at echocardiographic examination are based on VARC-2 criteria (37), and aimed at exploring prosthetic valve-performance and ventricular performance. A minimum set of echocardiographic data will be considered, as follows: 1) left ventricular (LV) function (EF% based on Simpson’s method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade (defined as mild, moderate or severe based on several different echocardiographic indexes as regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local institutional policies). Further assessment of “intra-prosthetic”, “peri-prosthetic” or “combined intra+peri-prosthetic” regurgitation will be added.

Short-Form 8 SF-8 Health Survey questionnaire: will be based on eight questionnaire items reported in Table 4 (51). This examination will be administered before surgery, at hospital

discharge, at 30-days, at 6 months, at 1 year, yearly thereafter up to the 5th-year of follow-up, then at follow-up closure (10th year).

ETHICS AND DISSEMINATION

The study is approved by the local Institutional Review Boards/Ethical Committees, according to local or national guidelines for approval of registry studies. Patient’s informed consent will be always obtained.

This multicenter, prospective open registry is designed with the aim of investigating a number of controversial issues regarding current treatment-options and risk factors for the surgical therapy of SAVS with or without CAD. Several studies and information are expected to derive from the data collected in the registry. These data will provide further knowledge on the mechanisms leading to adverse events during or after surgery for SAVS and help their prevention, thus allowing a “tailored” surgical approach for the treatment of this disease.

Several studies are planned at the moment:

Primary study:

- 1) A 5-year study comparing all-cause mortality between SAVR and surgical TAVR. We expect to report a 10% superiority of SAVR vs. TAVR according to sample size calculation and literature data (7). This study will also report echocardiographic data, functional status, quality of life, incidence of cardiovascular mortality, reinterventions on the aortic valve, and incidence of structural valve deterioration between “all-comers” surgical TAVR and SAVR. The study is expected 6 years after the start of data collection and it is aimed at being presented in a major European cardiology journal

Secondary sub-studies

- 2) An observational study providing results of the different surgical techniques to treat SAVS - in terms of “all-cause” and “cardiovascular” mortality, major morbidity and VARC-2

follow-up outcome analysis - at the end of the 5th-year follow-up of the last patient enrolled. We aim at present this study in a major cardio-thoracic surgical Congress and publish it in a Congress-satellite Journal. This study is expected after 6 years from the start of data collection.

- 3) A study comparing early and 5-year follow-up outcome of mechanical vs. biological prostheses in young population (<70 years of age). Propensity-matching and risk-adjusted analyses will be performed. It is aimed at being presented in a major American journal of the cardiology field. This study is expected after 6 years from the start of data collection.
- 4) A study comparing early and 5-year follow-up outcome of stented vs. stentless vs. sutureless bioprotheses vs. surgical TAVR in small annuli (≤ 21 mm). Propensity-matching and risk-adjusted analyses will be performed. Post-hoc analysis will help elucidate between-group differences. It is aimed at being presented in a major European cardiology journal of the cardiology field. This study is expected after 6 years from the start of data collection.
- 5) A study comparing early and 5-year follow-up outcome of sutured (both stented and stentless) bioprotheses vs. sutureless bioprotheses. Propensity-matching and risk-adjusted analyses will be performed. It is aimed at being presented in a major American or European journal of the cardiology field. This study is expected after 6 years from the start of data collection.
- 6) A 5-year outcome study comparing SAVR vs. surgical TAVR in intermediate-risk patients. Propensity-matching and risk-adjusted analyses will be performed. This study is aimed at being presented in a major European journal of the cardiology field. It is expected after 6 years from the start of data collection.
- 7) A 3-year outcome study comparing different surgical techniques of TAVR (i.e. trans-apical vs. trans-aortic vs. trans-axillary approach). Propensity-matching and risk-adjusted analyses will be executed if baseline differences are identified between the 3 subpopulations. Post-hoc statistical analyses will identify outcome-differences between the 3 subgroups. This

- study is aimed at being presented in a European journal of the field. This study is expected after 4 years from the start of data collection.
- 8) A 5-year outcome study resembling the previous one for final outcome data. This study is aimed at being presented in a major American journal of the field . It is expected after 6 years from the start of data collection.
- 9) An interim-study analyzing 30-day outcome of the first 4000 patients enrolled. This study is expected after 1 year from the start of data collection. It is aimed at being presented in a major European cardio-thoracic Meeting and satellite journal.
- 10) A study analyzing 30-day outcome and 1-year follow-up outcome of the first 4000 SAVR-patients enrolled. Sub-group analyses will be aimed at compare different surgical accesses (i.e. sternotomy vs. mini-sternotomy vs. mini-thoracotomy). Propensity-matching, risk-adjusted and post-hoc analyses will be done appropriately to nullify potential bias in the interpretation of the results, and to compare the results of each surgical subgroup. This study is expected after 2 years from the start of data collection. It is aimed at being presented in a major European cardio-thoracic Congress and satellite journal
- 11) A study analyzing the 5-year outcome after SAVR+CABG vs. TAVR±PCI (regardless of the surgical access for SAVR and TAVR) in patients admitted with contemporary critical aortic stenosis and coronary disease. Propensity-score and risk-adjusted analyzed will be done as appropriate for a correct interpretation of data. Particular attention will be focused on the role of “incomplete revascularization” and of different techniques of “staged TAVR and PCI” in the transcatheter group. This study is expected after 6 years from the start of data collection. It is aimed at being presented in a major European cardio-thoracic Congress and satellite journal
- 12) A 10-year study comparing all-cause and cardiovascular mortality, echocardiographic data, functional status, quality of life, incidence of reinterventions on the aortic valve, and incidence of structural valve deterioration between SAVR and surgical TAVR. This study is

expected after 11 years from the start of data collection and it is aimed at being presented in a major European cardiology journal

- 13) A 10-year study comparing all-cause and cardiovascular mortality, echocardiographic data, functional status, quality of life, incidence of reinterventions on the aortic valve and incidence of structural valve deterioration between SAVR with “sutured” valves and SAVR with “sutureless” valves. This study is expected after 11 years from the start of data collection and it is aimed at being presented in a major cardiology journal

Further studies aimed at peculiar sub-group analyses are not considered at this moment, but the E-AVR Steering Committee will evaluate any study/sub-study proposal from any researcher involved in the Registry, and accept/reject it by vote after review and discussion about its feasibility.

Therefore, research findings from the E-AVR registry will be disseminated among the scientific community. They will be presented at international congresses and published in peer reviewed international journals in the fields of cardiac surgery and cardiology. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship. Data collection, analysis and writing process will be monitored by the Steering Committee of the E-AVR, which is made up of the Principal Investigator and a local Representing Member from each of the participating centres. It is expected that periodical E-AVR Steering Committee meetings will occur, every 6 months for the first 2 years, yearly thereafter up to the end of follow-up. A complete list of the E-AVR Collaborators is reported in Appendix. The Members of the Steering Committee will take responsibility for the quality of data through local audit.

Investigators will be eligible for authorship if they contribute substantially to study planning, data collection, data analysis and interpretation, writing and critical review of the manuscripts. Two authors per centre will be included as main authors of each study. As a member of the Steering Committee, the local Representing Member will take any decisions on co-authorship related to

his/her centre on the basis of the above criteria. Those researchers who plan a sub-study, interpret the analysis and write the article will be the first and last authors of the study. Analyses will be performed and/or monitored by an independent Central Core Statistic Laboratory. When an article is submitted to a journal with a maximum number of co-authors, the Steering Committee will decide on the authors on the basis of their contribution to the design of the study, data collection, interpretation of data, writing, and critical review of the paper.

In the event of future merging with other contemporary registries (e.g. collecting data on concurrent interventional – i.e. percutaneous transfemoral, transcarotid or trans-axillary - TAVR procedures), the co-authorship of comparative studies (e.g. between surgical and interventional treatments) will be defined by the Steering Committees of the different registries involved. However, data will not be made available for sharing until after publication of the principal results of the study. Thereafter, anonymized individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements, and value for money. Anonymized data will be shared as long as the patient has agreed and consented to this. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research.

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COMPETING INTEREST STATEMENT

None to declare.

FIGURE LEGENDS

Figure 1. Flowchart of enrolment criteria and surgical techniques considered in the registry (CAD: coronary artery disease)

Figure 2. Flowchart of time-points for data collection

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M.D., Vasilis Babaliaros, M.D., Wilson Y. Szeto, M.D., Mathew R. Williams, M.D., Dean Kereiakes, M.D., Alan Zajarias, M.D., Kevin L. Greason, M.D., Brian K. Whisenant, M.D., Robert W. Hodson, M.D., Jeffrey W. Moses, M.D., Alfredo Trento, M.D., David L. Brown, M.D., William F. Fearon, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Wael A. Jaber, M.D., William N. Anderson, Ph.D., Maria C. Alu, M.M., and John G. Webb, M.D., for the PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2016;374:1609-20.

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AUTHOR'S CONTRIBUTIONS:

F. Onorati: Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

R. Gherli: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

G. Mariscalco: Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

E. Girdauskas: Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

E.O. Quintana: Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

F. Santini: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

M. De Feo: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

S. Sponga: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

P. Tozzi: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

M. Bashir: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

A. Perrotti: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

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A. Pappalardo: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

V.G. Ruggieri: Conception of the study, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

G. Santarpino: drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspects of the study

M. Rinaldi: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

C. Antona: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

F. Nicolini: Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing

TABLE 1: Stages of renal failure.

Stages	eGFR level (mL/min/1.73 m ²)
1	90 or above
2	89 to 60
3a	59 to 44
3b	44 to 30
4	29 to 15
5	Less than 15 or on dialysis

TABLE 2: New York Heart Association functional classes.

<i>Class</i>	<i>Definition</i>
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest
IV	Severe limitations. Experiences symptoms even while <i>at rest</i> . Mostly bedbound patients

TABLE 3: Definition criteria of type V myocardial infarction.

Baseline condition	Definition
1. In patients with normal baseline CK-MB or cTn (I or T)	The peak CK-MB measured within 48 hours of the procedure rises to $\geq 10 \times$ the local laboratory upper limit of normal (ULN), or to $\geq 5 \times$ ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the procedure rises to $\geq 70 \times$ the local laboratory ULN, or $\geq 35 \times$ ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB.
2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Table 4: SF-8TM Health Survey

Date _____ Name _____

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. For each of the following questions, please mark an [x] in the one box that best describes your answer.

I. Overall, how would you rate your health during the past 4 weeks?

Excellent	Very Good	Good	Fair	Poor	Very Poor
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II. During the past 4 weeks, how much did physical health problems limit your physical activities (such as walking or climbing stairs)?

Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities
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III. During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?

Not at all	Very little	Somewhat	Quite a lot	Could not do daily work
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IV. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
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V. During the past 4 weeks, how much energy did you have?

Very much	Quite a lot	Some	A little	None
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VI. During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?

Not at all	Very little	Somewhat	Quite a lot	Could not do social activities
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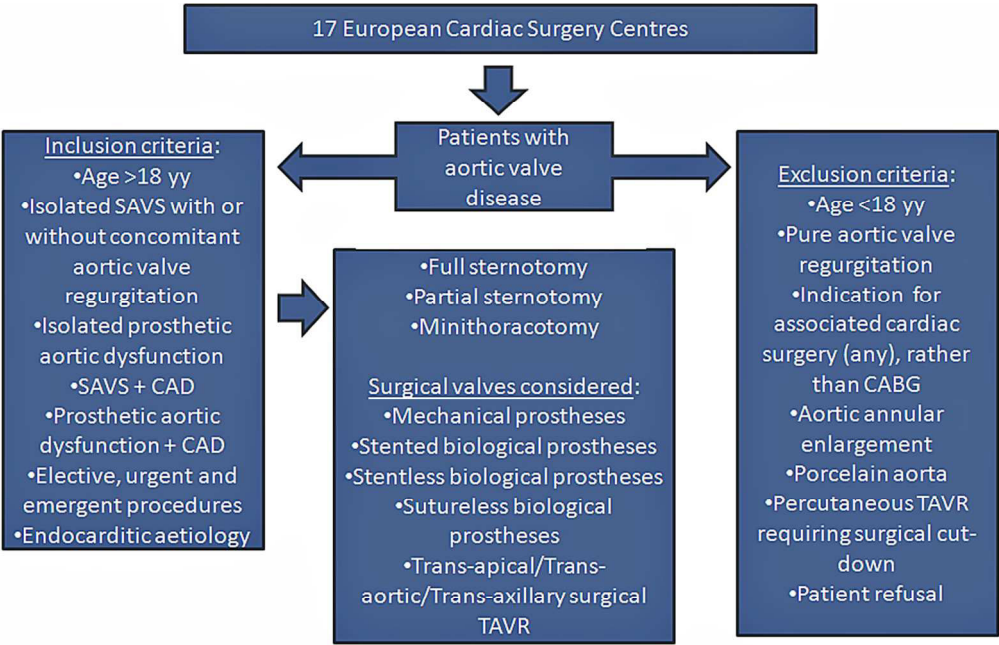
VII. During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?

Not at all Slightly Moderately Quite a lot Extremely

VIII. During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

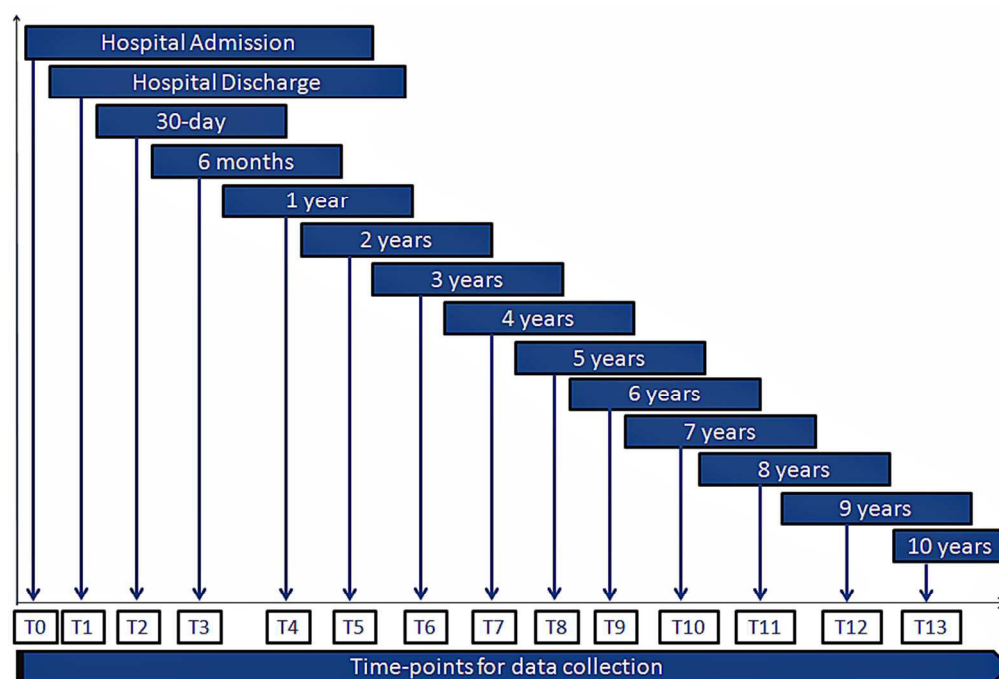
Not at all Very little Somewhat Quite a lot Could not do daily activities

For peer review only



Flowchart of enrolment criteria and surgical techniques considered in the registry (CAD: coronary artery disease)

81x56mm (300 x 300 DPI)



Flowchart of time-points for data collection

81x56mm (300 x 300 DPI)

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Appendix. E-AVR Collaborators

1. **Tiziano Gherli, MD** – Div. Cardiac Surgery, University of Parma, Parma, Italy
2. **Giuseppe Faggian, MD** and **Livio San Biagio, MD** – Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy
3. **Francesco Musumeci, MD** – Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy
4. **Hermann Reichenspurner, MD** – Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany
5. **Manuel Castellà, MD** – University Hospital Clinic, Barcellona, Spain
6. **Antonio Salsano, MD** – Cardiac Surgery Unit, University of Genova, Genoa, Italy
7. **Alessandro Della Corte, MD PhD** and **Ciro Bancone, MD** - Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy
8. **Ugolino Livi, MD** - Cardiothoracic Department, University Hospital of Udine, Udine, Italy
9. **Nicola Masala, MD** and **Gavin J. Murphy, MD** - Department of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK
10. **Sidney Chocron, MD PhD** - Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France
11. **Giuseppe Gatti, MD** and **Luca Maschietto, MD** - Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy
12. **Stefano Salizzoni, MD** – Dpt of Cardiac Surgery, Torino University Hospitals, Turin, Italy
13. **Francesco Pollari, MD** - Cardiovascular Center, Klinikum Nürnberg – Paracelsus Medical University, Nuremberg, Germany
14. **Alessandro Di Cesare, MD** - Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN, Hopital Robert Debre’, Reims, France

SPIRIT CHECKLIST

1. Outcomes comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)
2.
 - a. ClinicalTrials.gov # NCT03143361
 - b. WHO Dataset specifications:
 - i. European Aortic Valve Registry (E-AVR); protocol n. 1
 - ii. Registration date: May 3, 2017
 - iii. ClinicalTrials.gov # NCT03143361
 - iv. Fundings: none
 - v. University of Parma, Parma, Italy
 - vi. None
 - vii. Prof. Francesco Nicolini, Div. Cardiac Surgery, University of Parma, Parma, Italy; email: francesco.nicolini@unipr.it; Via A. Gramsci 14 – 43126 - Parma (PR) – Italy
 - viii. Prof. Francesco Nicolini, Div. Cardiac Surgery, University of Parma, Parma, Italy; email: francesco.nicolini@unipr.it; Via A. Gramsci 14 – 43126 - Parma (PR) – Italy
 - ix. Dr. Francesco Onorati, Div. Cardiac Surgery, University Hospitals in Verona, Verona, Italy; email: francesco.onorati@aovr.veneto.it; Piazzale Stefani, 1 – 37100 - Verona (VR) – Italy
 - x. European Aortic Valve Surgery Registry
 - xi. Outcome comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)
 - xii. Italy, United Kingdom, France, Germany, Spain, Switzerland
 - xiii. Surgical treatment of aortic valve stenosis with or without concomitant coronary artery disease
 - xiv. The following interventions will be analyzed:
 1. Surgical Aortic Valve Replacement (SAVR) via:
 - a. Full Sternotomy
 - b. Mini-thoracotomy
 - c. Mini-sternotomy
 - d. Stented prostheses (mechanical and biological)
 - e. Stentless prostheses (biological)
 - f. Sutureless prostheses (biological)
 2. Surgical Transcatheter Aortic Valve Replacement (TAVR) via:
 - a. Mini-thoracotomy via trans-apical route
 - b. Mini-sternotomy via trans-aortic route
 - c. Mini-thoracotomy via trans-aortic route
 - d. Sub-clavear via trans-axillary route
 - xv. Inclusion criteria: Isolated severe aortic valve stenosis (SAVS) with or without concomitant aortic valve regurgitation; isolated prosthetic aortic dysfunction; SAVS + coronary artery disease (CAD); prosthetic aortic dysfunction + CAD; age >18 yy; elective, urgent and emergent procedures; endocarditic aetiology; exclusion criteria: concomitant mitral valve surgery, tricuspid valve surgery, aortic surgery, atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG); surgical aortic annular enlargement; porcelain aorta; pure aortic valve regurgitation; percutaneous TAVR requiring surgical cut-down; patient refusal
 - xvi. Prospective non-randomized open cohort study
 - xvii. 1st October, 2017
 - xviii. A minimum of 8000 patients in 2 years of enrolment
 - xix. Waiting for the start of enrolment
 - xx. All-cause mortality (any death, either of cardiovascular and non cardiovascular nature) at 5 year from enrolment. Checked by linking with regional Social Security

Death and Events Master files, by phone contact with general practitioner, and in case of absent/missing data by direct phone contact with families.

xxi.

1. *All-cause mortality* (any death, either of cardiovascular and non cardiovascular nature) at 30-day, 6-month, 1-year and yearly up to 10-year (5-year excluded) follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with families.
2. *Cardiovascular mortality* (the sum of: 1) death due to proximate cardiac cause, e.g. myocardial infarction, cardiac tamponade, worsening heart failure, low cardiac output syndrome, etc.; 2) death caused by non-coronary vascular conditions, e.g. pulmonary embolisms, stroke, aortic rupture or vascular dissection, etc; 3) all procedure-related deaths, including those related to a complication of the procedure or a treatment for a complication of the procedure; 4) all valve-related deaths including valve dysfunction - structural or non-structural - and other valve-related adverse events; 5) sudden or unwitnessed death) at 30-day, 6-month, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with families.
3. *30-day Type 5 myocardial infarction*: defined according to the recent criteria defined by Moussa et al. (J Am Coll Cardiol 2013; 62:1563-1570). Assessed at 30-day. Collected from hospital registries.
4. *30-day stroke*: classified as 1) ischemic; 2) haemorrhagic; 3) unknown, according to VARC-2 consensus (Eur J Cardio Thorac Surg 2012; 42: S45–S60). The diagnosis and nature of stroke will be supported by CT or MRI imaging and confirmed by a consultant neurologist. Assessed at 30-day. Collected from hospital registries.
5. *Early repeated intervention for index intervention failure*: This refers to any surgical or percutaneous procedure on the aortic valve and/or the coronary arteries, performed during the same hospital stay for any prosthesis-related or graft-related complication. These events will be marked as occurring or not, and further detailed in their nature (“valvular early procedure”, “coronary early procedure” or “coronary + valvular early procedure”). Further details will be collected as explanatory notes. Assessed at 30-day. Collected from hospital registries.
6. *Postoperative need for prolonged use of inotropes*: this refers to the use of inotropes for >72 hours after the index operation. The type, dose and duration of administered inotropes will be also collected. Assessed at 30-day. Collected from hospital registries.
7. *Need for intra-aortic balloon pump (IABP)*: intra- or postoperative insertion of an intra-aortic balloon pump device. Assessed at 30-day. Collected from hospital registries.
8. *Need for extracorporeal mechanical oxygenation (ECMO)*: intra- or postoperative insertion of an extracorporeal mechanical pump/oxygenation device. Assessed at 30-day. Collected from hospital registries.
9. *Surgical site infection*: wound complications are graded according to the Centre for Disease Control and Prevention definitions of surgical site infections (Infect Control Hosp Epidemiol 1999; 20: 250-278). Any surgical site infection occurring within three months after surgery will be considered as a postoperative wound infection. Assessed at 30-day and 3 months after procedure. Collected from hospital registries and outpatient clinic registries.
10. *Bleeding*: classified as 1) life-threatening or disabling bleeding; 2) major bleeding; 3) minor bleeding, according to the recent definition criteria

- reported by the VARC-2 document (Eur J Cardio Thorac Surg 2012; 42: S45–S60). Assessed at 30-day. Collected from hospital registries.
11. *Blood losses at 12 hours*: the amount of postoperative blood losses from mediastinal drainages 12 hours after surgery. Intraoperative blood losses are not taken into account. Nadir haemoglobin and nadir haematocrit will be collected. Assessed at 30-day. Collected from hospital registries.
 12. *Use of blood products during hospitalization for the index surgical procedure*: total amount of blood products (detailed as red packed cells, fresh frozen plasma, or platelet concentrates) from the beginning of surgery to the day of discharge. Assessed at 30-day. Collected from hospital registries.
 13. *Resternotomy for bleeding*: Any reoperation for postoperative bleeding, regardless of concomitant hemodynamic problems. Assessed at 30-day. Collected from hospital registries.
 14. *Pericardial effusion requiring treatment*: any pericardial effusion requiring interventional treatment (e.g. pericardiocentesis, subxifoid drainage, resternotomy, etc) due to cardiac tamponade, sub-tamponade, or hemodynamic instability refractory to conservative treatment-strategies. Assessed at 30-day. Collected from hospital registries.
 15. *Acute renal failure*: severity of acute renal failure after surgery will be graded in AKIN stages from 1 to 3, according to VARC-2 criteria (Eur J Cardio Thorac Surg 2012; 42: S45–S60). Assessed at 30-day. Collected from hospital registries.
 16. *Atrial fibrillation*: any new paroxysmal/permanent atrial fibrillation episode requiring or not requiring pharmacological or electrical cardioversion attempts. Number of recurrences will be also collected. Assessed at 30-day. Collected from hospital registries.
 17. *Cardiac conduction disturbances*: defined as a new left bundle branch block, right bundle branch block, or AV-block (1st, 2nd or 3rd degree). Diagnosis will be based on official medical reports from a consultant cardiologist. In case of progressive bradi-arrhythmias, the evolution of the arrhythmias will be collected. Assessed at 30-day. Collected from hospital registries.
 18. *Need for permanent PMK*: collected as a dichotomic variable. Type of permanent pacing set-up (e.g. AAI, VVI, DDD, etc) will be collected. Assessed at 30-day. Collected from hospital registries.
 19. *Length of stay in the intensive care unit*: number of hours spent in the intensive care unit from surgery. Readmissions to intensive care unit will be considered and included in the number estimation. Assessed at 30-day. Collected from hospital registries.
 20. *Length of in-hospital stay*: number of days spent into hospital (ICU-stay will be added) from the day of surgery to hospital discharge to any other hospital ward, rehabilitation unit or home. Assessed at 30-day. Collected from hospital registries.
 21. *Follow-up stroke*: any focal or global neurological syndrome occurring after discharge and caused by ischemia and/or haemorrhage not resolving within 24 hours. The diagnosis and nature of stroke will be made on the basis of findings from brain CT, or MRI, or based on the medical report of a consultant neurologist. Assessed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
 22. *Follow-up myocardial infarction*: any myocardial infarction occurring after discharge and requiring medical, interventional or surgical treatment occurring after discharge. Assessed at 6-months, 1-year and yearly up to 10-

- year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
23. *Follow-up re-intervention on the aortic valve*: re-intervention is defined as any surgical or percutaneous interventional treatment that replaces (or repairs) an aortic prosthesis implanted at the time of the index procedure which is dysfunctional for either structural or non-structural reasons. Analyzed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
24. *Follow-up aortic valve-related adverse event*: this includes: 1) embolism; 2) valve thrombosis; 3) bleeding events; 3) structural valve deterioration; 4) paravalvular leakage; 5) operated valve endocarditis; 6) haemolysis, based on the definitions of current Guidelines for reporting mortality and morbidity after cardiac valve interventions (J Thorac Cardiovasc Surg 2008; 135: 732-8). Analyzed at 30-days, 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
25. *Follow-up repeated revascularization*: any CABG and/or PCI performed after discharge for coronary graft dysfunction and/or valve-related coronary complication. Any revascularization due to the progression of an untreated subcritical (at the time of the index procedure) coronary target will not be considered. Analyzed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
26. *Composite outcome*: according to VARC-2 definitions (Eur J Cardio Thorac Surg 2012; 42: S45–S60), this includes: 1) device success (absence of procedural mortality with correct positioning of a single prosthesis and with intended performance of the prosthesis); 2) early safety at 30 days (composite endpoint of all-cause mortality, all strokes, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary obstruction requiring intervention, major vascular complication or valve-related dysfunction requiring repeat procedure); 3) clinical efficacy after 30 days (composite endpoint of all-cause mortality, all strokes, hospitalization for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV, valve related dysfunction); 4) time-related valve safety (composite endpoint of structural valve deterioration requiring repeat procedure, prosthetic valve endocarditis, thrombosis, thrombo-embolic events or valve-related VARC bleeding). Analyzed at 30-days, 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
27. *MACCE* (defined as composite end-point including any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, repeated revascularization) at 30-day, 6-month, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master

files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with families.

28. Quality of life (QoL; defined according to Short Form-8 questionnaire) at hospital admission, at 30-day, 6-months, 1-year and yearly up to 10-year follow-up. QoL will be assessed during follow-up visits at outpatient clinics or, if other methods are not possible, by telephone interview.
29. Echocardiographic data of prosthesis performance. Data collected at echocardiographic examination are based on VARC-2 criteria (37). A minimum set of echocardiographic data will be considered: 1) left ventricular (LV) function (EF% based on Simpson's method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade (defined as mild, moderate or severe based on several different echocardiographic indexes as regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local institutional policies). Further assessment of "intra-prosthetic", "peri-prosthetic" or "combined intra+peri-prosthetic" regurgitation will be added. Echocardiographic data will be assessed at hospital admission, before hospital discharge, at 30 days after surgery, 6 months, 1 year after implantation, and yearly thereafter up to the follow-up closure (10th year) by Institutional 3rd level certified Echocardiographic Laboratories.

3. Protocol n.1.2.17 of 12th August, 2017

4. Funding: None

5.

- a. *Francesco Nicolini, MD PhD, Associate Professor*. Div. Cardiac Surgery, University of Parma, Parma, Italy; Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing, member of the E-AVR Steering Committee
Francesco Onorati, MD PhD. Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee
Riccardo Gherli, MD. Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee
Giovanni Mariscalco, MD PhD. Dpt. of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK; Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee
Evaldas Girdauskas, MD. Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany, Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee
Eduardo Obrador Quintana, MD. University Hospital Clinic, Barcellona, Spain; Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee
Francesco Santini, MD Full Professor. Cardiac Surgery Unit, University of Genova, Genoa, Italy; Conception and design of the study, drafting the paper, critically revising the paper,

final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Marisa De Feo, MD PhD Full Professor. Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Sandro Sponga, MD PhD. Cardiothoracic Department, University Hospital of Udine, Udine, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Piergiorgio Tozzi, MD Associate Professor. Cardiac Surgery Unit, Centre Hopitalier Universitaire Vaudois, Lausanne Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Mohammad Bashir, MD. Division of Cardiac Surgery, St. Barth Hospital NHS, London, UK. Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Andrea Perrotti, MD. Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France. Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Aniello Pappalardo, MD. Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy. Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Vito Giovanni Ruggieri, MD Professor. Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN, Hopital Robert Debre', Reims, France; Conception of the study, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Giuseppe Santarpino, MD. Cardiovascular Center, Klinikum Nürnberg – Paracelsus Medical University, Nuremberg, Germany. Drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspects of the study, member of the E-AVR Steering Committee

Mauro Rinaldi, MD PhD Full Professor. Department of Cardiac Surgery, Torino University Hospitals, Turin, Italy. Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Carlo Antona, MD Full Professor. Department of Cardiac Surgery, Ospedale Sacco, Milan, Italy; Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee.

Tiziano Gherli, MD Full Professor. Div. Cardiac Surgery, University of Parma, Parma, Italy; Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing, member of the E-AVR Steering Committee

Giuseppe Faggian, MD PhD Full Professor. Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; Conception of the study, design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee.

b. Prof. Francesco Nicolini, Div. Cardiac Surgery, University of Parma, Parma, Italy; email: francesco.nicolini@unipr.it; Via dell'Università n.12 – 43121 - Parma (PR) – Italy.

c. Funders: None. Sponsor roles: no external sponsor for the trial. The PI (Prof. F. Nicolini) has active participation in study design, collection and management of data (analysis of data

performed by an external Statistical Core Laboratory), interpretation of data, writing reports, and decision to submit the reports for publication; however, no ultimate Authority over any of these activities

- d. Coordinating Centre composition: Professor Francesco Nicolini, MD, and Professor Tiziano Gherli, MD; Div. Cardiac Surgery University of Parma. Roles: coordination of the Registry, active participation in study design, collection and management of data (analysis of data performed by an external Statistical Core Laboratory), interpretation of data, writing reports, and decision to submit the reports for publication. No ultimate Authority over any of these activities. Responsibility: coordination of the Registry, E-AVR Steering Committee adherence to its roles.

Steering Committee: Composition: F. Onorati, F. Nicolini, R. Gherli, G. Mariscalco, E. Girdauskas, E.O. Quintana, F. Santini, M. De Feo, S. Sponga, P. Tozzi, M. Bashir, A. Perrotti, A. Pappalardo, V.G. Ruggieri, G. Santarpino, M. Rinaldi, C. Antona, T. Gherli, G. Faggian.

Roles: Generate the sequence to maintain anonymized the entire set of data, protect confidentiality about patient identity before, during and after the trial, and retain data in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.

Take responsibility of data collection, data monitoring through local auditing, endpoint adjudication, and writing process; evaluation of sub-study proposal from researchers involved in the Registry, and accept/reject it by vote after review and discussion about its feasibility; take any decisions on co-authorship on the basis of individual contribution to the design of the study, data collection, interpretation of data, writing, and critical review of the paper; establish periodical E-AVR Steering Committee meetings; maintain a copy of the complete database.

Take responsibility of further checking, reviewing, correcting and merging in case of incomplete or contradictory data, and in case of data without identification code.

Data Management: apart from a local data auditing (responsibility of the E-AVR Steering Committee), the Central Core Statistical Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) will take responsibility of storage, analysis and auditing of data every six-months

6.

- a. The prevalence of severe aortic valve stenosis (SAVS) correlates with age, and its treatment is expected to increase parallel to the improved life-expectancy reported in Western Countries (1-2). Traditional surgical aortic valve replacement (SAVR) has been the gold standard of treatment for decades, with well-documented benefits in terms of symptom improvement and survival (3-4). Recent technological advances allowed interventional and surgical transcatheter aortic valve replacements (TAVR), which proved to be effective alternatives to traditional SAVR, in both high-risk and intermediate-risk patients (5-12). Therefore, SAVR and TAVR represent nowadays the standard surgical armamentarium for aortic valve replacement. Alternative surgical approaches, based on the concept of TAVR (13,14), have in fact been developed. There are on the market two types of “sutureless” valves (i.e. Sorin Perceval and Edwards Intuity) at the moment - aimed at reducing some surgical drawbacks such as cross-clamp time and myocardial ischemia-reperfusion injury (13,15-20) – but it is possible that new “sutureless” valves will enter the market in the next future. Moreover, different mini-thoracotomy and mini-sternotomy approaches to SAVR have been widely adopted by the surgical community - with both “sutured” and “sutureless” valves - in order to reduce surgical trauma, systemic inflammatory response, and major organ morbidity (13,15,16). Various different combinations of minimally invasive accesses and the use of last-generation valves have been reported to date (14,17,18). But despite early enthusiasm about preliminary results with these technological improvements, none of these techniques has yet replaced traditional SAVR in standard surgical practice, mainly because reporting of results of these alternative techniques tends to be biased by single-centre design, limited sample-size, and the strict inclusion/exclusion criteria of the published studies (13,14).

Another “hot topic” in this debate relates to valve durability, given that the long-term durability of both TAVR and sutureless valves is as yet unknown. Indeed, standard “sutured” surgical valves demonstrated excellent durability, both in the very-long term and in very-young adults below the 65-year cut-off age (21-23), which is still the threshold for biological valves recommended by European Society of Cardiology (ESC) / European Association for CardioThoracic Surgery (EACTS) guidelines (24). This issue is of particular interest, given that the use of TAVR has increased in younger intermediate-risk patients, despite recent caveats relating to early degeneration of TAVR (25,26). Similarly, improved life-expectancy has led to a growing number of patients with degenerated dysfunctioning aortic bioprostheses requiring surgical treatment. Again, surgical aortic prosthetic replacement (SAPR) has been traditionally considered the only treatment strategy for these patients, given the excellent results, recently confirmed by several studies (27,28). Again, transcatheter treatments (“valve-in-valve”) have recently demonstrated comparable or sometimes superior results in redo-scenarios (29). Therefore, data on the efficacy, safety and durability of these technological improvements are essential for providing “strong” statements in future guidelines, and for evaluating the extension of these techniques to low-risk and young patients in the future. Finally, it is well known that critical coronary artery disease (CAD) often coexists with SAVS. Although the standard treatment option for these patients has traditionally been SAVR plus coronary artery bypass grafting (CABG), the introduction of TAVR and minimally invasive surgical alternatives has considerably changed the available options, paving the way to combined less-invasive SAVR+CABG and/or TAVR±PCI (either before, during or after the surgical procedure) (30-34). Again, there is a great deal of confusion on the topic, and there are unanswered questions on the efficacy and safety of these options, as well as on what to expect from late follow-up when compared to the standard practice of SAVR+CABG.

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- b. Robust early and follow-up data on the safety and efficacy of surgical TAVR, last-generation sutureless surgical valves, and minimally-invasive approaches compared with standard SAVR, with or without a contemporary (surgical or interventional) treatment of concurrent CAD, are still lacking for a real-world large population of patients at variable surgical risk. Such data is urgently required for the correct allocation of therapy in daily surgical practice. Furthermore, data on quality of life and functional echocardiographic results with different surgical alternatives might similarly help physicians in decision-making in local "Heart Teams". Data from a multicentre, real-world, open registry enrolling all patients with SAVS±CAD consecutively referred to several Centres at different European latitudes should help to answer some of these open questions.
- In particular, comparative analyses between mid-to-long term outcome of SAVR vs surgical TAVR will clarify the mid-to-long term prognosis associated with these 2 different techniques (risk of death, risk of reintervention, functional class, quality of life, etc)
- Comparison between sutured and sutureless aortic prostheses, since hospitalization to 10-year follow-up, will elucidate if (and how much) the use of rapid-deployment valves is superior compared to standard techniques
- Comparisons of minimally invasive approaches and full-sternotomy, since hospitalization to 10-year follow-up, will define the safety and efficacy of the former over the latter techniques.
7. The principal objective of the study is the 5-year comparison between outcome after SAVR and outcome after surgical TAVR: we hypothesize to report a 10% superiority in terms of all-cause mortality in favor of SAVR vs. TAVR.
 8. The trial is a prospective registry-based observational cohort study, enrolling all patients fulfilling inclusion criteria (all comers), aimed at a superiority design (10% superiority of SAVR vs. TAVR in 5-year all-cause mortality)
 9. Settings: University hospitals and 3rd level community hospitals (France, Germany, Italy, Spain, Switzerland, United Kingdom).
 10. Inclusion criteria: Isolated severe aortic valve stenosis (SAVS) with or without concomitant aortic valve regurgitation; isolated prosthetic aortic dysfunction; SAVS + coronary artery disease (CAD); prosthetic aortic dysfunction + CAD; age >18 yy; elective, urgent and emergent procedures; endocarditic aetiology. Exclusion criteria: concomitant mitral valve surgery, tricuspid valve surgery, aortic surgery, atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG); surgical aortic annular enlargement; porcelain aorta; pure aortic valve regurgitation; percutaneous TAVR requiring surgical cut-down; patient refusal.
- Individuals who will perform the interventions: surgeons
11.
 - a. Surgical aortic valve replacement (SAVR) with any of the following surgical accesses:
 - i. Full sternotomy
 - ii. Mini-thoracotomy
 - iii. Mini-sternotomy
 And with any of the following prostheses:

- OR

- iv. Mini-thoracotomy via trans-apical route
- v. Mini-sternotomy via trans-aortic route
- vi. Mini-thoracotomy via trans-aortic route
- vii. Sub-clavear via trans-axillary route

- b. Criteria for discontinuing, withdrawing or modifying allocated intervention: intraoperative demonstration of unexpected porcelain aorta; unplanned need for concomitant mitral valve surgery, and/or tricuspid valve surgery, and/or aortic surgery, and/or atrial fibrillation surgery, and/or any other associated cardiac surgical procedure (with the exception of CABG); unplanned need for a surgical aortic annular enlargement
- c. N.A.: there are no strategies to improve adherence to protocols: this because any intraoperative and postoperative strategy/protocol is allowed (observational nature of the study), and then recorded in the Registry.
- d. Concomitant interventions that are prohibited during the trial are: planned concomitant mitral valve surgery, tricuspid valve surgery, aortic surgery, atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG); planned surgical aortic annular enlargement.

- i. *5-year all-cause mortality* (time to event; proportion; 5-year time-point)

- ii. *Cardiovascular mortality* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- iii. *All-cause mortality* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- iv. *Type 5 myocardial infarction* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- v. *Stroke* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- vi. *Early repeated intervention for index intervention failure* (time to event; proportion; 30-day).
- vii. *Postoperative need for prolonged use of inotropes* (final value; proportion; 30-day time-point)
- viii. *Need for intra-aortic balloon pump* (time to event; proportion; 30-day time-point)
- ix. *Need for extracorporeal mechanical oxygenation* (time to event; proportion; 30-day time-point)
- x. *Surgical site infection* (time to event; proportion; 30-day and 6-month time-points)
- xi. *Bleeding* (final value; proportion; 30-day time-point)
- xii. *Blood losses at 12 hours* (final value; proportion; 30-day time-point)
- xiii. *Use of blood products during hospitalization for the index surgical procedure* (final value; proportion; 30-day time-point)
- xiv. *Resternotomy for bleeding* (time to event; proportion; 30-day time-point)

- xv. *Pericardial effusion requiring treatment* (time to event; proportion; 30-day time-point)
- xvi. *Acute renal failure* (time to event; proportion; 30-day time-point)
- xvii. *Atrial fibrillation* (time to event and final value; proportion; 30-day time-point)
- xviii. *Cardiac conduction disturbances* (time to event; proportion; 30-day time-point)
- xix. *Need for permanent PMK* (time to event; proportion; 30-day time-point)
- xx. *Length of stay in the intensive care unit* (final value; proportion; 30-day time-point)
- xxi. *Length of in-hospital stay* (final value; proportion; 30-day time-point)
- xxii. *Follow-up re-intervention on the aortic valve*: (time to event; proportion; 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxiii. *Follow-up aortic valve-related adverse event* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point).
- xxiv. *Follow-up repeated revascularization* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxv. *Device success* (time to event; proportion; 30-day)
- xxvi. *Early safety at 30 days* ((time to event; proportion; 30-day)
- xxvii. *Clinical efficacy after 30 days* (time to event; proportion; 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxviii. *Time-related valve safety* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxix. *MACCE* (time to event; proportion; 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxx. *Quality of life* (change from baseline; median; hospital discharge, 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxxi. *Echocardiographic data of prosthesis performance* (change from baseline; median; hospital discharge, 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)

13. 2- year of enrolment, starting on October, 1st 2017 and ending on Septemebr 30th 2019; 10-year of follow-up (closure on September 30th 2029). Data collection pertaining the hospital course. Follow-up time points: 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year.

Hospital admission	Hospital course	Discharge	30-day	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8 year	9 year	10 year
Enrollment Baseline data Quality of life (QoF) Echocardiographic parameter s (Echo)	Data pertaining surgery and postoperative care. Hospital outcome adjudication	Type of discharge QoF Echo	Outcomes adjudication (O.A.) QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	Primary outcome O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo

14. A minimum of 8000 patients enrolled over 2 years. The primary aim of the study is a 5-year comparison between SAVR and surgical TAVR: we hypothesize to report a 10% superiority in terms of all-cause mortality in favor of SAVR vs TAVR. Given the PARTNER TRIAL 5-year all-cause mortality risk (Lancet 2015;385:2477-84) of 67.8% after TAVR and 62.4% after SAVR – accepting

a type 1 error of 5% - the overall number of patients needed to achieve 80% power (1-beta) for a mortality odds of 1.1 (10% mortality difference) is 2866 patients (i.e. 1433 patient/group). Therefore, the expected number of 8000 patients is far beyond the requested sample size of the primary objective of the trial, and further accounts for risk-adjustment methodologies and the expected 1.5% (historical data) of lost to follow-up.

15. This is an all-comers registry-based cohort study. Historical data from the participating Centres demonstrate that at least 8000 patients (far beyond the number requested by sample size calculation) will be collected in 2 years, using an “all-comers” strategy

16. N.A.

17. N.A.

18.

- a. Data will be prospectively collected in a dedicated Database. Data pertaining hospitalization will be collected by hospital registries, whereas variables and outcome events occurring after the index hospital discharge will be collected from outpatient clinics at the individual Institutions, and linking with regional Social Security Death and Events Master files. Events and outcome variables will be adjudicated after agreement of two local E-AVR Investigators, and collected at local Institutions. In the event of controversy on outcome adjudication between the two local E-AVR Investigators, the outcome will be adjudicated after a final consult inside the E-AVR Steering Committee. Collection of data is under the responsibility of the Steering Committee local member at each participating Centre. Data will be audited from the Central Core Laboratory on a regular basis, as reported previously. In case of absent/missing data, variables and events will be collected by direct phone contact with general practitioners, and only if persistently missed by phone contact with patients and families. The Local E-AVR Steering Committee member is responsible for a continuous active auditing of local data. The Central Core Statistical Lab will perform 6-month external auditing by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator and E-AVR Steering Committee for further data checking and merging. Incomplete or contradictory data with patient identification code will be sent from Central Core Statistical Lab to the E-AVR Steering Committee local member for further data checking, review, correction and merging.

Laboratory parameters: baseline levels of haemoglobin, haematocrit, platelets, blood glucose, HbA1c, C-reactive protein, TT-INR, creatinine, e-GFR and albumin will be collected.

Units of measurement: Laboratory data will be collected according to fixed units of measurement in order to avoid any problem stemming from differences in units used by the various participating centres, during data merging and analysis. The fixed units of measurement are reported in the dedicated CRF datasheet.

Short-Form 8 SF-8 Health Survey questionnaire: will be based on eight questionnaire items reported in Table 4 of the protocol.

Echocardiographic data: Data collected at echocardiographic examination are based on VARC-2 criteria (Eur J Cardio Thorac Surg 2012; 42: S45–S60). A minimum set of echocardiographic data will be considered: 1) left ventricular (LV) function (EF% based on Simpson’s method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade (defined as mild, moderate or severe based on several different echocardiographic indexes as regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local institutional policies). Further assessment of “intra-prosthetic”, “peri-prosthetic” or “combined intra+peri-prosthetic” regurgitation will be added.

- b. Active explanation to patients and families about the importance of adherence to follow-up visits for final interpretation of data – with its consequences on Guidelines and current daily practice - will be pursued.
- It is expected that linking with regional Social Security Death and Events Master files and using phone contacts with general practitioners will lead to ascertain at least the following follow-up outcome data: 1) All-cause mortality and cardiovascular mortality; 2) MACCE; 3) Reinterventions on the aortic valve; 4) Valve-related adverse events; 5) Repeated revascularization; 6) Clinical efficacy after 30-days; 7) Time-related valve safety.
- On the opposite, it is expected a 100% completeness of data related to hospitalization.
19. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Centre (2 letters), the initial of name (1 letter) and surname (1 letter), and the date of birth (dd.mm.yyyy) (e.g. Mr. John Smith, born on February 18th, 1953; enrolled in London = LOJS18021953). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity.
- Every Centre will be anonymized by identification with a capital letter. The correspondence between centres and capital letters will only be known by the PI of the study. The Central Core Statistical Laboratory analyzing the data will be blinded towards the surgical teams. The Central Core Statistical Laboratory will take responsibility of data managing. Data will be audited from the Central Core Laboratory on a regular basis, as reported previously. All data will be retained in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. See “Data Management and monitoring” paragraph of the protocol.
- 20.
- a. Continuous variables will be reported as mean and standard deviation or median and interquartile range, as appropriate. Dichotomous and nominal variables will be reported as counts and percentages. Univariate analysis will be performed using the Mann-Whitney U test and Student’s t-test for continuous variables (pending the not-normal or normal distribution respectively), the Kruskal-Wallis test (independent multilevel ordinal variables), Wilcoxon test (for paired variables), Fisher exact test and Chi-square test (for dichotomous/nominal variables) and Kaplan-Meier test (for time-dependent dichotomous variables). Multivariable analyses will be performed using logistic regression method (for categorical dependent variable), classification tree analysis (for target variables with a discrete set of value), linear regression (for continuous dependent variable) and ordinal regression methods (for ordinal dependent variable), as well as Cox-proportional hazards method (to test the effects of covariates on time-dependent dichotomous variables). Significant differences between study groups will be adjusted by using propensity score as covariate or by one-to-one propensity score matching. Matching will be performed using a caliper width of 0.2 of the standard deviation of logit of the propensity score.
- b. Multiple propensity score adjusted analysis will be performed in case of multiple study groups. A Bayesian hierarchical approach will be used in the case of significant variability between centres. Sensitivity analysis will be executed using complete-case analysis. Interim analyses are planned at different time-points (see Ethics and Dissemination), with critical p-values corrected according to the Armitage-McPherson adjustment
- c. Missing values will be replaced and estimated using multiple imputations.
- 21.
- a. Data Monitoring Committee is not needed because the E-AVR Steering Committee and the Central Core Statistical Lab will take responsibilities of DMC. In particular, data will be collected into a dedicated datasheet with predefined variables. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Centre (2 letters), the initial of name (1 letter) and surname (1 letter), and the date of birth (dd.mm.yyyy) (e.g. Mr. John Smith, born on February 18th, 1953; enrolled in London = LOJS18021953). It is responsibility of the E-AVR Steering Committee local

member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity. All data will be retained in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. The E-AVR Steering Committee local member has also the responsibility for a continuous auditing of local data, by double-checking and monitoring of data quality and their completeness. Storage, analysis and further auditing of data will be then accomplished by the independent Central Core Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy). External auditing of the dataset will be performed every six months by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator and E-AVR Steering Committee for further data checking and merging. Incomplete or contradictory data with patient identification code will be sent from Central Core Statistical Lab to the E-AVR Steering Committee local member for further data checking, correction and merging. Both the E-AVR Steering Committee (with its members) and Central Statistical Core Lab are free from competing interests (the trial has no sponsor).

- b. The following interim-analyses have been established:
1. A 3-year outcome study comparing different surgical techniques of TAVR (i.e. trans-apical vs. trans-aortic vs. trans-axillary approach); propensity-matching and risk-adjusted analyses will be executed if baseline differences are identified between the 3 subpopulations; post-hoc statistical analyses will identify outcome-differences between the 3 subgroups
 2. An interim-study analyzing 30-day outcome of the first 4000 patients enrolled.
 3. A study analyzing 30-day and 1-year outcome of the first 4000 SAVR-patients enrolled. Sub-group analyses will be aimed at compare different surgical accesses (i.e. sternotomy vs. mini-sternotomy vs. mini-thoracotomy); propensity-matching, risk-adjusted and post-hoc analyses will be done appropriately to nullify potential bias in the interpretation of the results, and to compare the results of each surgical subgroup.

The results of these interim analyses will be available to all the E-AVR Investigators for data interpretation, with the aim to write “dedicated” scientific papers on these 3 topics. Given that these 3 interim-analyses do not deal with the primary objective of the registry (5-year outcome comparison between SAVR and TAVR), all these results will not have any impact on the possible termination of the trial. Furthermore, investigated treatments (SAVR and TAVR) are standards of care according to Current Guidelines and Good clinical practice, therefore no stopping guidelines for the premature termination of the trial can be foreseen at the moment.

22. N.A.: the trial is an observational registry-based cohort study, with collection of data representing standard surgical practice and state-of-the-art perioperative care for cardiac surgical interventions. There are no randomized interventions nor treatments administered per-protocol, therefore no “adverse events” or “unintended effects” directly related to the conductance of the trial can be foreseen.
23. The Local E-AVR Steering Committee local member is responsible for a continuous active auditing of local data. The Central Core Statistical Lab will perform 6-month external auditing – independent from investigators (no sponsor exists) - by checking the data of a minimum of 40% of the patients.
24. Ethical Committee (EC) approvals from the PI Centre (University of Parma) and from University of Verona Centre have been already obtained. The PI’s Ethical Committee approval has been already sent – at the time of writing – to all the ECs of E-AVR participating Centres, based on the requests of the local ECs. All the requests for EC-approval of the other E-AVR participating Centres therefore have been already sent. It is expected to receive all the EC approvals within September 2017. In the unlucky (and unlikely, given the observational nature of the registry) event that a Centre will not receive EC approval, that Centre will not participate in the Registry.
25. Important protocol modifications will be discussed inside the E-AVR Steering Committee and -if accepted – communicated to all the E-AVR investigators, as well as to all the ECs of the E-AVR

participating Centers by means of “amendment requests”. Only in case of approvals from all ECs the modification will enter the protocol.

26.
 - a. Written informed consent will be obtained from the patient or patient’s authorized representative prior to enrolment in the Registry. In case of emergent surgery, informed consent will be collected from the patient’s family (or legal representative) before surgery, as well as from the patient after surgery (if unable to give it before intervention). This consent will be waived in case of death or severe neurological damage precluding adequate postoperative patient informed consent. The study will be conducted in accordance with the provisions of the Declaration of Helsinki.
 - b. N.A.: no ancillary studies are planned
27. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Centre (2 letters), the initial of name (1 letter) and surname (1 letter), and the date of birth (dd.mm.yyyy) (e.g. Mr. John Smith, born on February 18th, 1953; enrolled in London = LOJS18021953). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity. Each participating centre will be anonymized by identification with a capital letter. The correspondence between centres and capital letters will only be known by the PI of the study. The Central Core Laboratory analyzing the data will be blinded towards the surgical teams.
28. No financial and/or competing interests for principal investigators, for the overall trial and each study site
29. The final dataset is only available to the Central Statistical Core Lab. However, the entire sets of the performed statistical analyses of the primary study and of secondary sub-studies will be available to all E-AVR researchers for the clinical interpretation of data. There is the agreement between E-AVR Investigators and Central Statistical Core Lab that preclude the access of final dataset to all the E-AVR Investigators.
30. N.A.: given the observational nature of this prospective registry-based cohort study, no ancillary or post-trial care is scheduled, and no harm is expected from the participation to the registry
31.
 - a. Research findings from the E-AVR registry will be disseminated among the scientific community. They will be presented at international congresses and published in peer reviewed international journals in the fields of cardiac surgery and cardiology. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship. Data collection, analysis and writing process will be monitored by the Steering Committee of the E-AVR, which is made up of the Principal Investigator and a Representing Member from each of the participating centres. It is expected that periodical E-AVR Steering Committee meetings will occur, every 6 months for the first 2 years, yearly thereafter up to the end of follow-up. In the event of future merging with other contemporary registries (e.g. collecting data on concurrent interventional – i.e. percutaneous transfemoral, transcarotid or trans-axillary - TAVR procedures), the co-authorship of comparative studies (e.g. between surgical and interventional treatments) will be defined by the Steering Committees of the different registries involved. However, data will not made available for sharing until after publication of the principal results of the study. Thereafter, anonymized individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed used of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements, and value for money. Anonymized data will be shared as long as the patient has agreed and consented to this. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research.

- b. Investigators will be eligible for authorship if they contribute substantially to study planning, data collection, data analysis and interpretation, writing and critical review of the manuscripts. Two authors per centre will be included as main authors of each study. As a member of the Steering Committee, the local Representing Member will take any decisions on co-authorship related to his/her centre on the basis of the above criteria. Those researchers who plan a sub-study, interpret the analysis and write the article will be the first and last authors of the study. When an article is submitted to a journal with a maximum number of co-authors, the Steering Committee will decide on the authors on the basis of their contribution to the design of the study, data collection, interpretation of data, writing, and critical review of the paper.
- c. No plan for granting public access to the full protocol, participant-level dataset and statistical code has been considered

32. PARTICIPANT INFORMATION LEAFLET

E-AVR: a Prospective European Multicenter Study on Aortic Valve Replacement

Introduction

You are being invited to take part in a clinical research study. However, before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Taking part in research is voluntary and your medical care will not be affected if you decide not to take part.

If anything is not clear or you would like more information, do not hesitate to ask your research doctor or another member of the research team when you come into hospital (also see contact details at the end of this leaflet).

Talk to others about the study if you wish, such as friends or relatives and take time to decide. If you would like to take part, you will be asked to confirm this before your operation, during your admission or at follow-up after discharge by signing a separate consent form.

What is the purpose of the study?

Severe aortic valve stenosis (abbreviation: SAVS) is a life-threatening disease in which the valve is blocked by the progressive degeneration of its tissue. The same situation is encountered some years after the implantation of a biologic aortic prosthesis, due to the progressive inflammation of prosthetic tissues (biologic prosthetic degeneration). Both conditions are usually treated with the replacement of the patient's failing aortic valve (or prosthesis) with an artificial prosthesis (surgical aortic valve replacement, abbreviation: SAVR, and surgical prosthetic valve replacement, abbreviation: SPVR). For decades the standard of care has been represented by performing this surgery through a surgical incision of the entire sternum (sternotomy) and with the aid of the so called heart lung machine (i.e., the heart is arrested during the central part of the operation, and vital functions are sustained with this machine). Recently, new surgical techniques have been developed. Indeed, it is possible to proceed to SAVR via different surgical skin incisions (sternotomy, partial sternotomy, small thoracotomy) but always using heart-lung machine; or it is possible to replace the failing valve with new biological prostheses - crimped on a catheter - implanted on the beating heart through small skin incisions (the latter called transcatheter aortic valve replacement, abbreviation: TAVR).

Native/prosthetic aortic valve replacement is one of the most commonly performed operation in cardiac surgery. Around 100,000 AVR procedures are performed in Europe every year. As with all types of surgery, it carries a risk of complications, usually minor, but there is also a risk of serious complications such as stroke, heart attack or even death. Together with other European centers we want to create a large database (registry) of patients affected by SAVS and undergoing surgical substitution of the failed native/prosthetic aortic valve (named E-AVR Registry) as we think that collection and analysis of data on risk factors, operative techniques, post-operative treatment and secondary prevention strategies will improve treatment and reduce the risk of early and late complications.

Why have I been invited?

You have been invited to take part because you are going to have or you already had an aortic valve replacement. Like you hundreds of patients across Europe will be invited to take part.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide and if you take part you are free to withdraw at any time. If you choose not to take part or to withdraw from the research, you do not have to give

any reason for your decision. The operation performed and the care you will receive after will be exactly the same whether you take part in the study or not.

What will happen to me if I take part?

You will be asked to give written consent to take part in the study and you will be given a copy of the consent form and this information leaflet to keep. After discharge we will collect data regarding your pre-operative clinical status, operation and post-operative course. The data collected will be made anonymous prior to be entered into a large European database and shared with other researchers across Europe. Personal identifiable information will not be shared and will remain strictly confidential.

What are the possible disadvantages and risks of taking part?

We do not think that taking part in the study will expose you to any risks or disadvantages. You may be contacted in the future and asked a number of questions regarding your health as a result of cardiac surgery.

What are the possible benefits of taking part?

We think that the information from this research will help us to improve treatment and ameliorate the early and late outcomes for patients having aortic valve replacement (AVR) in the future.

What will happen to the results of the study?

The results of the study will be published in medical journals or shared during medical meetings. Thereafter, anonymous individual patient data will be made available for secondary research, after a proper research approval. You will not be identified in any way. If you would like to receive the results of the study written in plain English, after the research has finished, please contact the study team on the numbers provided at the end of this leaflet.

Further information and contact details:

If you have any concerns or questions about this study please contact the research team on the number or email address provided below. Please use the contact details only for questions about the E-AVR study project. Alternatively you can discuss these with a member of the research team who will come to see you before your operation. Please feel free to ask any further questions before deciding to take part in the study, or at any time during it.

Contact details:

If you want further information contact Dr X X (xxxxxxxxxxxxxxxxxx) or email (xxxxxxxxxxxx).

Other members of the Research Team (email):

Dr. X X (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)

Dr. X X (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)

CONSENT FORM

Name of Researcher: Dr X X

Name of the study: E-AVR: a Prospective European Multicenter Study on Aortic Valve Replacement

I have had the opportunity to consider the information provided, ask questions and have had these answered satisfactorily	<input type="checkbox"/>
I understand that my participation in the E-AVR registry is voluntary and that I am free to withdraw at any time, without giving any reason	<input type="checkbox"/>
I understand that the information collected will remain anonymous prior to be shared with other European centres that will only have access to non identifiable information	<input type="checkbox"/>

I understand that in the future I may be contacted to be asked questions regarding my clinical status in relation to my AVR operation	<input type="checkbox"/>
I agree to take part in the E-CABG registry	<input type="checkbox"/>

I, the undersigned, have read, understood and agree to the above conditions

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

33. N.A.

BMJ Open

Outcomes comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)

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Manuscripts

Outcomes comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)

F. Onorati¹, R. Gherli², G. Mariscalco³, E. Girdauskas⁴, E.O. Quintana⁵, F. Santini⁶, M. De Feo⁷, S. Sponga⁸, P. Tozzi⁹, M. Bashir¹⁰, A. Perrotti¹¹, A. Pappalardo¹², V.G. Ruggieri¹³, G. Santarpino¹⁴, M. Rinaldi¹⁵, Silva RRG¹⁶, F. Nicolini¹⁷, on behalf of E-AVR Collaborators.

¹Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; ²Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy; ³Department of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK; ⁴Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany; ⁵University Hospital Clinic, Barcellona, Spain; ⁶Cardiac Surgery Unit, University of Genova, Genoa, Italy; ⁷Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy; ⁸Cardiothoracic Department, University Hospital of Udine, Udine, Italy; ⁹Cardiac Surgery Unit, Centre Hospitalier Universitaire Vaudois, Lausanne; ¹⁰Division of Cardiac Surgery, St. Barth Hospital NHS, London, UK; ¹¹Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France; ¹²Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy; ¹³Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN, Hopital Robert Debre', Reims, France; ¹⁴Cardiovascular Center, Klinikum Nürnberg – Paracelsus Medical University, Nuremberg, Germany; ¹⁵Department of Cardiac Surgery, Torino University Hospitals, Turin, Italy; ¹⁶Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy; ¹⁷Div. Cardiac Surgery, University of Parma, Parma, Italy

Corresponding Author: Francesco Onorati, MD PhD – Div. Cardiac Surgery, Dpt. of Surgery, University of Verona Medical School - Piazzale Stefani n.1 – 37126 – Verona, Italy. Phone: 0039 (0)45 8121945; Fax: 0039 (0)45 8123308; Email: francesco.onorati@aovr.veneto.it

ABSTRACT

Introduction: Traditional and transcatheter surgical treatments of severe aortic valve stenosis (SAVS) are increasing in parallel with the improved life-expectancy. Recent randomized trials (RCTs) reported comparable or non-inferior mortality with transcatheter treatments compared to traditional surgery. However, RCTs have the limitation of being a mirror of the predefined inclusion/exclusion criteria, without reflecting the “real clinical world”.

Technological improvements have recently allowed the development of minimally invasive surgical accesses and the use of sutureless valves, but their impact on the clinical scenario is difficult to assess because of the monocentric design of published studies and limited sample-size. A prospective multicentre registry including all patients referred for a surgical treatment of SAVS (traditional, through full-sternotomy; minimally-invasive; or transcatheter; with both “sutured” and “sutureless” valves) will provide a “real-world” picture of available results of current surgical options, and will help to clarify the “grey zones” of current guidelines.

Methods and analysis: E-AVR is a prospective observational open registry designed to collect all data from patients admitted for SAVS, with or without coronary artery disease, in 16 cardiac surgery Centres located in six countries (France, Germany, Italy, Spain, Switzerland, and United Kingdom). Patients will be enrolled over a 2-year period and followed-up for a minimum of 5 years to a maximum of 10 years after enrolment. Outcome definitions are concordant with VARC-2 criteria and established guidelines. Primary outcome is 5-year all-cause mortality. Secondary outcomes aim at establishing “early” 30-day all-cause and cardiovascular mortality, as well as major morbidity, and “late” cardio-vascular mortality, major morbidity, structural and non-structural valve complications, quality of life and echocardiographic results.

Ethics and dissemination: The study protocol is approved by Local Ethics Committees. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship.

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STRENGTHS AND LIMITATIONS OF THIS STUDY:

- The protocol addresses the important question of which surgical treatment offers the most benefits in the management of patients with severe aortic valve stenosis, with or without concomitant coronary artery disease.
- The expected large sample size will guide sub-analyses aimed at identify specific patient characteristics and different risk-profiles, which are better served with alternative surgical techniques.
- The minimum 5-year and maximum 10-year follow-up will provide answers about the mid-to-long term safety and efficacy of recent surgical innovations (i.e. sutureless valves, minimally invasive approaches, surgical TAVR), whose follow-up data are still lacking in current literature
- The present multicentre registry has clearly established aim, inclusion and exclusion criteria, short-term and follow-up primary and secondary endpoints, as well as state-of-the-art methods for data collection and endpoints definition
- Limitations include variations in postoperative and follow-up management, which are based on local Institutional policies, and lack of blinding between the central statistical core-lab performing the analyses and the employed surgical techniques
- The absence of any external sponsor certainly limits research resource allocation, but also guarantees the certainty for the absence of any bias or conflict of interest related to the investigated topics

INTRODUCTION

The prevalence of severe aortic valve stenosis (SAVS) correlates with age, and its treatment is expected to increase parallel to the improved life-expectancy reported in Western Countries (1-2). Traditional surgical aortic valve replacement (SAVR) has been the gold standard of treatment for decades, with well-documented benefits in terms of symptom improvement and survival (3-4). Recent technological advances allowed interventional and surgical transcatheter aortic valve replacements (TAVR), which proved to be effective alternatives to traditional SAVR, in both high-risk and intermediate-risk patients (5-12). Therefore, SAVR and TAVR represent nowadays the standard surgical armamentarium for aortic valve replacement.

Alternative surgical approaches, based on the concept of TAVR (13,14), have in fact been developed. There are on the market two types of “sutureless” valves (i.e. Sorin Perceval and Edwards Intuity) at the moment - aimed at reducing some surgical drawbacks such as cross-clamp time and myocardial ischemia-reperfusion injury (13,15-20) – and it is possible that new “sutureless” valves will enter the market in the next future. Moreover, different mini-thoracotomy and mini-sternotomy approaches to SAVR have been widely adopted by the surgical community - with both “sutured” and “sutureless” valves - in order to reduce surgical trauma, systemic inflammatory response, and major organ morbidity (13,15,16). Various different combinations of minimally invasive accesses and the use of last-generation valves have been reported to date (14,17,18). But despite early enthusiasm about preliminary results with these technological improvements, none of these techniques has yet replaced traditional SAVR in standard surgical practice, mainly because reporting of results of these alternative techniques tends to be biased by single-centre design, limited sample-size, and the strict inclusion/exclusion criteria of the published studies (13,14).

Another “hot topic” in this debate relates to valve durability, given that the long-term durability of both TAVR and sutureless valves is as yet unknown. Indeed, standard “sutured” surgical valves demonstrated excellent durability, both in the very-long term and in very-young adults below the

65-year cut-off age (21-23), which is still the threshold for biological valves recommended by European Society of Cardiology (ESC) / European Association for CardioThoracic Surgery (EACTS) guidelines (24). This issue is of particular interest, given that the use of TAVR has increased in younger intermediate-risk patients, despite recent caveats relating to early degeneration of TAVR (25,26).

Similarly, improved life-expectancy has led to a growing number of patients with degenerated dysfunctioning aortic bioprostheses requiring surgical treatment. Again, surgical aortic prosthetic replacement (SAPR) has been traditionally considered the only treatment strategy for these patients, given the excellent results, recently confirmed by several studies (27,28). Again, transcatheter treatments ("valve-in-valve") have recently demonstrated comparable or sometimes superior results in redo-scenarios (29). Therefore, data on the efficacy, safety and durability of these technological improvements are essential for providing "strong" statements in future guidelines, and for evaluating the extension of these techniques to low-risk and young patients in the future.

Finally, it is well known that critical coronary artery disease (CAD) often coexists with SAVS. Although the standard treatment option for these patients has traditionally been SAVR plus coronary artery bypass grafting (CABG), the introduction of TAVR and minimally invasive surgical alternatives has considerably changed the available options, paving the way to combined less-invasive SAVR+CABG and/or TAVR±PCI (either before, during or after the surgical procedure) (30-34). Again, there is a great deal of confusion on the topic, and there are unanswered questions on the efficacy and safety of these options, as well as on what to expect from late follow-up when compared to the standard practice of SAVR+CABG.

Robust early and follow-up data on the safety and efficacy of surgical TAVR, last-generation sutureless surgical valves, and minimally-invasive approaches compared with standard SAVR, with or without a contemporary (surgical or interventional) treatment of concurrent CAD, are still lacking for a real-world large population of patients at variable surgical risk. Such data is urgently required for the correct allocation of therapy in daily surgical practice. Furthermore, data on quality

of life and functional echocardiographic results with different surgical alternatives might similarly help physicians in decision-making in local “Heart Teams”. Data from a multicentre, real-world, open registry enrolling all patients with SAVS±CAD consecutively referred to several Centres at different European latitudes should help to answer some of these open questions. Here, we describe the rationale and the study protocol of the European Aortic Valve Registry (E-AVR), a multicenter prospective observational open registry on aortic valve surgical practice.

METHODS AND ANALYSIS

Rationale of the study and aim

Improvements in surgical treatment of cardiac diseases can be obtained with the implementation of current techniques and the development of new methods, based on information from large clinical datasets (35). The main strength of a prospective clinical open registry is the high external validity, given that data are collected in the settings of standard clinical practice. Moreover, large sample size enables a better estimation of event rates, and allows the investigation of hard endpoints and outcomes, by means of a wide population of patients from different institutions and with extremely limited exclusion criteria.

Importantly, clinical registries may provide data on long-term outcomes occurring after the study period of a trial (35). They are more practical than randomized controlled trials, require fewer resources, and have less stringent inclusion and exclusion criteria for patient enrolment. Finally, clinical findings from registries have even more significance when patient-populations derive from different geographic areas, with heterogeneous referral pathways, baseline clinical characteristics, and perioperative treatment strategies. All these features substantiate the concept of “a real world practice” underlying any “registry-study”.

Therefore, the rationale of this European multicenter observational open registry is to prospectively collect data on baseline characteristics, treatment options, perioperative management and postoperative outcome of all patients consecutively undergoing surgical treatment of SAVS

(regardless of gradients, AVA or AVAi)±CAD or aortic prosthetic dysfunction±CAD at 16 European university or non-university tertiary hospitals located in six European countries (France, Germany, Italy, Spain, Switzerland, and United Kingdom). The complete list of E-AVR Collaborators is reported in the Appendix.

The primary aim of the study is a 5-year comparison between SAVR and surgical TAVR: we hypothesize to report a 10% superiority in terms of all-cause mortality in favor of SAVR vs TAVR. For the purpose of this study, patients will be consecutively enrolled for a 2-year period, and will be followed-up for a minimum of 5 years after the index surgical treatment. Maximum follow-up length will be 10 years after surgery.

The following surgical options will be considered:

- 1) SAVR with mechanical valves
- 2) SAVR with biological valves (either sutured or sutureless, stented or stentless)
- 3) Surgical TAVR (either transapical, trans-axillary, or transaortic)

Similarly, the following surgical approaches will be considered:

- 1) Full sternotomy
- 2) Mini-thoracotomy (either left-sided for TAVR or right-sided for SAVR)
- 3) Partial-sternotomy

Patient allocation to a specific surgical procedure will be based on the local Heart Team decision at each Institution, according to standard clinical practice and current guidelines (2).

A flow-chart of the enrolment criteria and of the surgical techniques considered in the registry is provided in Figure 1.

Criteria for registry-enrolment

The following inclusion and exclusion criteria will be considered:

Inclusion criteria

- Age >18 yy
- Isolated SAVS with or without concomitant aortic valve regurgitation

- Isolated prosthetic aortic dysfunction
- SAVS + coronary artery disease (CAD)
- Prosthetic aortic dysfunction + CAD
- Elective, urgent and emergent procedures
- Endocarditic aetiology

Exclusion criteria

- Patients undergoing concomitant mitral valve surgery, or tricuspid valve surgery, or aortic surgery (i.e. composite aortic valve and ascending aorta replacement with or without circulatory arrest), or atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG)
- Concomitant aortic root procedure (i.e. Bentall operation, David operation, homografts, autografts)
- SAVR with techniques of aortic annular enlargement
- Porcelain aorta
- Pure aortic valve regurgitation
- Percutaneous TAVR requiring surgical cut-down (i.e. failure to comply with a full percutaneous approach, thus configuring a “hybrid procedure”)
- Patient refusal

Patients will be recruited in a consecutive series from each institution, and their data collected in a dedicated on-line datasheet. The recruitment period will be 24 months, from 1st November 2017 to 30th October 2019. Every patient will be followed up at 30 days, 6 months, 1 year, and yearly thereafter, up to a minimum of 5 years after the index surgical procedure (Figure 2). Afterwards yearly follow-up will be closed at the completion of the 10th year from surgery for each patient. On the basis of historical cohort data of local institutions, we expect to enrol a minimum of 4000 patients at the end of the first year, and a minimum of 8000 patients at the end of the second year of enrolment.

Informed consent

Written informed consent will be obtained from the patient or patient's authorized representative prior to enrolment in the Registry. In case of emergent surgery, informed consent will be collected from the patient's family (or legal representative) before surgery, as well as from the patient after surgery (if unable to give it before intervention). This consent will be waived in case of death or severe neurological damage precluding adequate postoperative patient informed consent. The study will be conducted in accordance with the provisions of the Declaration of Helsinki. The study is registered in Clinicaltrials.gov. (No. NCT03143361)

Data management and monitoring

Data will be collected into a dedicated datasheet with predefined variables. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Country (2 letters), enrolling Centre (2 letters), and then consecutive number (considered at thousands)(e.g. Mr. XY, third patient enrolled in London = UKLO0003). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, the external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity.

All data will be retained in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.

Baseline characteristics, operative details and outcome data pertaining hospitalization will be prospectively collected from hospital registries. Variables and events occurring after the index hospital discharge will be collected from outpatient clinics at the individual Institutions, and linking with regional Social Security Death and Events Master files where available. In case of

absent/missing data, variables and events will be collected by direct phone contact with general practitioners, and only if persistently missed by phone contact with patients and families.

Events and outcome variables will be adjudicated centrally by a Central Core Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy). In the event of controversy on outcome adjudication, this will be discussed and adjudicated after a final consult between the Central Core Laboratory and the E-AVR Steering Committee.

Storage, analysis and auditing of data will be also accomplished by the independent Central Core Laboratory. Auditing of the dataset will be performed every six months by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator and E-AVR Steering Committee for further data checking and merging. Incomplete or contradictory data with patient identification code will be sent from Central Core Statistical Lab to the E-AVR Steering Committee local member for further data checking, review, correction and merging. The entire set of statistical analyses will be available to all E-AVR researchers for the interpretation of data.

Statistical methods

The Central Core Lab (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) will perform all the statistical analyses derived from this registry.

The sample size calculation is based on a recent published study (36), specifically on the 5-year all-cause mortality rate (24.6%) of the 620 intermediate risk patients, our target population, who underwent SAVR. We hypothesize that the 5-year mortality rate following SAVR is 10% inferior compared to the surgical TAVR, and calculate the sample size using a conservative one-sided log-rank test. Assuming that patients will enter the study uniformly over the 2 years accrual time, 5 years total follow-up time, 80% statistical power, 5% significance level and 1.5% (historical data) probability of patient’s right censoring occurs. The resulting sample size is 6493 subjects (3246 in the control group and 3247 in the treatment group). Therefore the expected number of 8000 patients

over a 2-year enrolment period is far beyond the requested sample size of the primary endpoint of the trial.

Continuous variables will be reported as mean and standard deviation or median and interquartile range, as appropriate. Dichotomous and nominal variables will be reported as counts and percentages. Univariate analysis will be performed using the Mann-Whitney U test and Student's t-test for continuous variables (pending the not-normal or normal distribution respectively), the Kruskal-Wallis test (independent multilevel ordinal variables), Wilcoxon test (for paired variables), Fisher exact test and Chi-square test (for dichotomous/nominal variables) and Kaplan-Meier test (for time-dependent dichotomous variables). Log-rank test will be used to compare the 5-year all-cause mortality rate between SAVR and surgical TAVR. Multivariable analyses will be performed using logistic regression method (for categorical dependent variable), classification tree analysis (for target variables with a discrete set of value), linear regression (for continuous dependent variable) and ordinal regression methods (for ordinal dependent variable). Cox-proportional hazards method will test the effects of covariates on time-dependent dichotomous variables; the model's proportional hazard assumption will be checked using the Schoenfeld residuals test. Significant differences between study groups will be adjusted by using propensity score as covariate or by one-to-one propensity score matching. Matching will be performed using a caliper width of 0.2 of the standard deviation of logit of the propensity score. Multiple propensity score adjusted analysis will be performed in case of multiple study groups. A Bayesian hierarchical approach will be used in the case of significant variability between centres.

Missing values will be replaced and estimated using multiple imputations. Furthermore, sensitivity analysis will be executed using complete-case analysis. Interim analyses are planned at different time-points (see Ethics and Dissemination). Critical p-values of accomplished interim analyses will be corrected according to the Armitage-McPherson adjustment (37).

Early and late endpoints

Outcome endpoints will be defined according to current guidelines, i.e. VARC-2 definitions (38) and Guidelines for reporting mortality and morbidity after cardiac valve interventions (39).

In more detail, the following outcome variables will be collected:

Primary outcome of the E-AVR registry: 5-year all-cause mortality

Secondary outcomes of the E-AVR registry: these will be dichotomized into “early” at 30-day (i.e. during hospitalization, at home if discharged, or during “rehab-hospitalization” at any time point if never discharged home) and “late” (after the patient is discharged home):

- 1) Early secondary outcomes: all-cause mortality, cardiovascular mortality, stroke, acute myocardial infarction (AMI) (40) , postoperative need for prolonged use of inotropes (>72 hours), postoperative need for intra-aortic balloon pump (IABP) or extracorporeal mechanical oxygenation (ECMO), surgical site infection, blood losses and use of blood products (during hospitalization for the index surgical procedure), nadir hematocrit, nadir hemoglobin, re-sternotomy for bleeding, atrial fibrillation (first event and number of events), cardiac conduction disturbances, need for new permanent pace-maker implantation, acute kidney injury (following AKIN classification), pericardial effusion requiring treatment, length of stay in the intensive care unit, length of in-hospital stay (for the index procedure), device success, early safety, clinical efficacy, time-related valve safety, echocardiographic data of prosthesis performance, early repeat surgery for failure of the index procedure (any “redo” before discharge home or to rehabilitation clinic).
- 2) Late secondary outcomes (collected starting from discharge to the end of the 10th year after the index procedure): cardiovascular mortality, all-cause mortality (from 1 to 4 years after surgery, then from 6 to 10 years), stroke, acute myocardial infarction, reintervention on the aortic prosthesis, repeat revascularization (either with percutaneous coronary intervention or CABG), prosthetic thrombosis, embolism, bleeding events, structural valve deterioration, paravalvular leakage, prosthetic endocarditis, need for permanent pacemaker, need for implantable cardioverter-defibrillator, MACCE (defined as a composite end-point including

any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, repeated revascularization), time-related valve safety, quality of life (QoL; defined according to Short Form-8 questionnaire; QoL will be assessed during follow-up visits at outpatient clinics or, if other methods are not possible, by telephone interview); echocardiographic data of prosthesis performance.

Echocardiographic data of prosthesis performance are defined according to the Valve Academic Research Consortium-2 definitions (38). All echocardiographic data will be collected from 3rd level nationally and/or internationally certified Institutional Echo Laboratories: 5% of these echocardiographic exams will be reviewed centrally (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) by third level certified echocardiographers. Collection of data is under the responsibility of the Steering Committee local member at each participating Centre. Data will be audited from the Central Core Laboratory on a regular basis, as reported previously.

Outcomes and their definition criteria are described in detail in the following section of this article.

Data collection

Participating Centre: Each participating Centre will be anonymized by identification with a capital letter. The correspondence between Centres and capital letters will only be known by the PI of the study. The Central Core Laboratory analyzing the data will be blinded towards the surgical teams.

Units of measurement: Laboratory data will be collected according to fixed units of measurement in order to avoid any problem stemming from differences in units used by the various participating centres, during data merging and analysis. The fixed units of measurement are reported in the dedicated CRF datasheet.

Laboratory parameters: baseline levels of haemoglobin, haematocrit, platelets, blood glucose, HbA1c, C-reactive protein, TT-INR and albumin will be collected.

Hypertension: arterial blood pressure > 140/90 mmHg or anti-hypertensive treatment.

Diabetes: diabetes mellitus requiring diet, oral or insulin treatment.

Preoperative creatinine levels: this parameter is obtained on the day before surgery and is expressed in $\mu\text{mol/L}$.

Chronic Kidney Disease: the severity of renal failure will be classified as shown in Table 1. It is stratified by the estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease Study Group modified formula (41). eGFR for calculation of the EuroSCORE II (42) will be estimated using the Cockcroft-Gault formula (43) according to the criteria of this risk scoring method.

Dialysis: peritoneal or hemo-dialysis before surgery.

Chronic obstructive pulmonary disease (COPD): any long-term use of bronchodilators or steroids for lung disease.

Oxygen therapy: long-term oxygen therapy for respiratory failure.

Liver disease: different degrees of liver failure stratified according to the Child-Pugh classification (44).

Active neoplasia: any active malignancy.

Preoperative stroke: any preoperative focal or global neurological syndrome caused by ischemia or haemorrhage not resolving within 24 hours.

Neurological dysfunction: disabling outcomes in ambulation and / or normal motor functions, according to EuroSCORE II definition (42).

Extracardiac arteriopathy: one or more of the following: claudication, carotid occlusion or >50% stenosis, amputation for arterial disease, previous or planned intervention on the abdominal aorta, limb arteries or carotids.

Preoperative ECG: sinus rhythm, or atrial fibrillation; or first degree AV block; or right bundle block; or left bundle block; or pacemaker rhythm.

Preoperative myocardial infarction: any preoperative myocardial infarction.

Previous vascular surgery: history of surgical or endovascular procedure of the thoracic or abdominal aorta and/or the iliac-femoral arteries.

Previous cardiac surgery: one or more previous cardiac operations requiring opening of the pericardium.

Type of previous cardiac surgery: description of previous cardiac operation.

Previous aortic valve replacement: description of prosthesis and date of operation.

Previous percutaneous coronary intervention: any previous percutaneous coronary intervention.

Etiology of aortic valve disease: native valve disease (degenerative; rheumatic; endocarditic) or prosthetic valve disease.

Endocarditis: any diagnosis of valve endocarditis made by the Heart Team and/or antibiotic treatment for endocarditis at the time of surgery. Subclassification into acute, subacute, and healed endocarditis based on Current Guidelines will be added (45).

Endocarditis etiology: microbe isolated for the diagnosis of endocarditis

NYHA functional classes: defined according to the criteria listed in Table 2 (46).

Aortic valve stenosis: severity of aortic valve stenosis before surgery will be graded as moderate or severe according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (47).

Aortic valve regurgitation: Severity of aortic valve regurgitation before surgery will be graded in classes from 0 to 3, and the grade of severity will be evaluated according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (47).

Associated critical coronary artery disease: presence of stenosis of at least 70% in any major epicardial coronary artery. Number of main vessels involved will be recorded. Patients with stenosis of the left main coronary artery will be considered as having at least two-vessel disease.

Associated left main coronary artery disease: Any LMSD > 50%

Mitral valve regurgitation: severity of concurrent mitral valve regurgitation - though not requiring surgery - will be graded in classes according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (47).

Left ventricular function: last measured left ventricular ejection fraction before surgery (in any case before induction of anesthesia).

Pulmonary hypertension: absent: <31 mmHg; moderate: 31-55 mmHg; severe: >55 mmHg, according to EuroSCORE II definition (42). Systolic pulmonary pressure will be estimated at echocardiography, at least before induction of anesthesia.

Preoperative echocardiography data: aortic valve area, peak transvalvular gradient, mean transvalvular gradient, aortic annulus diameter, maximum jet velocity (TTE) will be recorded.

Preoperative multislice CT scan data: annulus circumference; valvular area; calcium score (collected for all surgical TAVR, and only if available for other surgical techniques)

Diseased ascending aorta: any sign of diffuse atherosclerosis in the ascending aorta at palpation or epiaortic ultrasound (porcelain aorta is not considered).

Montgomery classification: if available, echocardiographic Montgomery classification of aortic atheromas will be provided.

Preoperative antithrombotic or antibiotic drug treatment: data on all antithrombotic drugs administered before surgery will be collected. The date of pause of drug treatment is the last day the patient received the drug. Data on any oral or intravenous antibiotics administered preoperatively without prophylaxis purpose, i.e. for any preoperative infectious condition, will be collected.

Elective surgery: elective procedure scheduled for stable aortic valve disease.

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3 *Urgent surgery*: procedure indicated by medical factors which require the patient to stay in hospital
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5 to have operation before discharge.
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8 *Emergency surgery*: procedure performed before the beginning of the working day after the
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10 decision to operate.
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13 *Frailty*: Preoperative patient's frailty is graded according to Geriatric Status Scale, as proposed by
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15 Rockwood et al (48).
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18 *Critical preoperative status*: ventricular tachycardia or ventricular fibrillation or aborted sudden
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20 death, preoperative cardiac massage, preoperative ventilation before anesthetic room, preoperative
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22 inotropes or IABP, preoperative acute renal failure (anuria or oliguria <10ml/hr), according to
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24 EuroSCORE II definition (42).
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28 *EuroSCORE II*: this risk score is calculated using the on-line calculator available at
29
30 <http://www.euroscore.org/calc.html> and reported as a percentage. The risk factors included in the
31
32 EuroSCORE II and collected in the E-AVR registry are defined according to the EuroSCORE II
33
34 criteria (42).
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37 *STS score*: this risk score is calculated using the on-line calculator available at
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39 <http://riskcalc.sts.org/stswebriskcalc/#/> and reported as a percentage. The risk factors included in the
40
41 STS score and collected in the E-AVR registry are defined according to the STS score criteria (49).
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43 *Surgical chest access*: classified as 1) full sternotomy; 2) minithoracotomy; 3) partial-sternotomy.
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46 *Aortic valve replacement data*: classified as 1) mechanical prosthesis; 2) stented biological
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48 prosthesis; 3) stentless biological prosthesis; 4) sutureless biological prosthesis; 5) trans-apical
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50 TAVR; 6) transaortic TAVR. The description of model and diameter of the prosthesis implanted and
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52 possible need for proctored procedure will also be collected.
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55 *Other intraoperative data*: type of cardioplegia and its temperature, duration of extracorporeal
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57 circulation (ECC), nadir temperature of ECC, and aortic cross-clamping time, need for re-aortic
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cross-clamping for any reason (paravalvular leak, coronary obstruction, annular rupture/hematoma, re-construction of CABG, etc), as well as details of TAVR implantation including sheath size, pre-implantation valvuloplasty, occurrence of valve-in-valve emergency procedure, the number of valves implanted, prosthesis migration, recapturing and re-positioning of the valve, post-procedural dilation, amount of contrast medium administered will be collected.

CABG details: Details of types of conduit and target vessel will be reported (e.g.: LIMA-LAD, RIMA-Dx, RA-MO. SV-DIAG): The following specifications for conduits will be used: LIMA: left internal mammary artery; RIMA: right internal mammary artery; RA: radial artery; GEA: gastro-epiploic artery; SV: saphenous vein. The following target acronyms will be used: DA: anterior descending; DIAG: diagonal; RX: right coronary (trunk); PDA: posterior descending; PL: postero-lateral; OM: obtuse marginal. In the event of sequential grafting, the prefix "seq" will be used before targets (e.g. LIMA-seq DIAG-DA)

Other CABG details: number of distal anastomoses, completeness of revascularization.

30-day all-cause mortality: defined as the sum of cardiovascular and non-cardiovascular, the latter defined as any death in which the primary cause is clearly related to another condition not contemplated by the definition “cardiovascular” (e.g. trauma, cancer, etc.), as in VARC-2 definition (38), but occurring within 30-days or during index procedure hospitalization if the postoperative length of stay is longer than 30 days.

30-day cardiovascular mortality: based on VARC-2 definition (38) and occurring within 30-days or during hospitalization for the index procedure if the postoperative length of stay is longer than 30 days. This includes: 1) death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure, low cardiac output syndrome, etc.); 2) death caused by non-coronary vascular conditions (e.g. pulmonary embolisms, stroke, aortic rupture or vascular dissection, etc); 3) all procedure-related deaths (including those related to a complication of the procedure or a treatment for a complication of the procedure); 4) all valve-related deaths including

valve dysfunction (structural or non-structural) and other valve-related adverse events; 5) sudden or unwitnessed death

Type 5 myocardial infarction: defined according to the recent criteria defined by Moussa et al. (50) (Table 3).

Atrial fibrillation: any new paroxysmal/permanent atrial fibrillation episode requiring or not requiring pharmacological or electrical cardioversion attempts. Number of recurrences will be also collected.

Cardiac conduction disturbances: defined as a new left bundle branch block, right bundle branch block, or AV-block (1st, 2nd or 3rd degree). Diagnosis will be based on official medical reports from a consultant cardiologist. In case of progressive bradi-arrhythmias, the evolution of the arrhythmias will be collected.

Need for permanent PMK: collected as a dichotomic variable. Type of permanent pacing set-up (e.g. AAI, VVI, DDD, etc) will be collected.

Postoperative neurologic damage: classified as: 0) absent; 1) disabling stroke; 2) non-disabling stroke; 3) TIA, based on definitions of VARC-2 consensus (38).

Stroke classification: 1) ischemic; 2) haemorrhagic; 3) unknown, according to VARC-2 consensus (38). The diagnosis and nature of stroke will be supported by CT or MRI imaging and confirmed by a consultant neurologist.

Prolonged use of inotropes (>72 hours): This refers to the use of inotropes for >72 hours after the index operation. The type, dose and duration of administered inotropes will be also collected.

Cardiogenic shock: postoperative critical hemodynamic condition requiring mechanical ventricular-assist devices or high-dose inotropes with evidence of peripheral malperfusion. Coexistence of a cardiac index < 1.8 l/min/m² despite adequate correction of all the coexisting preload, afterload, electrolyte and gas-analyses abnormalities will be pursued with the aid of different hemodynamic monitoring methods, according to local Institutional policies (e.g. echocardiography, Swan-Ganz catheter, PICCO, PRAM, Vigileo, etc.).

IABP: intra- or postoperative insertion of an intra-aortic balloon pump device.

ECMO: intra- or postoperative insertion of an extracorporeal mechanical pump/oxygenation device.

Bleeding: classified as 1) life-threatening or disabling bleeding; 2) major bleeding; 3) minor bleeding, according to the recent definition criteria reported by the VARC-2 document (38).

Blood loss 12 hours after surgery: the amount of postoperative blood losses from mediastinal drainages 12 hours after surgery. Intraoperative blood losses are not taken into account. Nadir haemoglobin and nadir haematocrit will be collected.

No. of transfused RBC units at hospital discharge: total amount of RBC units intra- and/or postoperatively transfused, from the beginning of surgery to the day of discharge.

No. of transfused fresh frozen plasma, pooled human plasma (Octaplas), and/or platelets units at hospital discharge: This refers to the transfusion of these blood products from the beginning of surgery to the day of discharge.

Reintervention for bleeding: any reoperation for postoperative bleeding, regardless of concomitant hemodynamic problems.

Reintervention for hemodynamic problems: any reoperation for hemodynamic instability. This can also be associated with excessive bleeding: in this case, both categories (“Reintervention for bleeding” and “Reintervention for hemodynamic problems”) will be marked.

Pericardial effusion requiring treatment: any pericardial effusion requiring interventional treatment (e.g. pericardiocentesis, subxifoid drainage, resternotomy, etc) due to cardiac tamponade, sub-tamponade, or hemodynamic instability refractory to conservative treatment-strategies.

Acute renal failure: severity of acute renal failure after surgery will be graded in AKIN stages from 1 to 3, according to VARC-2 criteria (38).

Highest postoperative creatinine level: the highest level of serum creatinine detected after surgery during the in-hospital stay. Creatinine levels will be reported in $\mu\text{mol/L}$

Renal replacement therapy: the need for renal replacement therapy will be dichotomized into “temporary” or “permanent” (the latter in the event of death while on renal replacement therapy, or if discharged on renal replacement therapy, or in case of life-long need). Type of renal replacement therapy (e.g. dialysis, CVVH, SCUF, etc.) will be also collected as a note.

Gastrointestinal complications: any gastrointestinal complication requiring endoscopy and/or surgical treatment. Endoscopic diagnostic procedures without any associated interventional procedure (diagnostic only) will not fit this definition.

Post-operative infection: classified as: 1) surgical site infection; 2) organ infection (respiratory, urinary, gastrointestinal infection); 3) systemic infection (sepsis) 4) index valve/device infection.

Wound complications are graded according to the Centre for Disease Control and Prevention definitions of surgical site infections (51). Any surgical site infection occurring within three months after surgery will be considered as a postoperative wound infection.

Early repeated intervention for index intervention failure: This refers to any surgical or percutaneous procedure on the aortic valve and/or the coronary arteries, performed during the same hospital stay for any prosthesis-related or graft-related complication. These events will be marked as occurring or not, and further detailed in their nature (“valvular early procedure”, “coronary early procedure” or “coronary + valvular early procedure”). Further details will be collected as explanatory notes.

Length of stay in the intensive care unit: number of hours spent in the intensive care unit from surgery. Readmissions to intensive care unit will be considered and included in the number. estimation.

Length of in-hospital stay: number of days spent into hospital (ICU-stay will be added) from the day of surgery to hospital discharge to any other hospital ward, rehabilitation unit or home.

Drug antithrombotic treatment at discharge: collected dichotomic (yes/no) for each of the following drugs: 1) vitamin-K antagonists; 2) new oral anticoagulants; 3) antiplatelets. Further details on type and dose of each drug will be added as a note.

Type of discharge: discharge will be categorized according to the Italian NIH classification, as follows: 1) death; 2) discharged home; 3) discharged to rehabilitation clinic; 4) voluntary discharge; 5) transferred to other hospital for acute complications; 6) transferred to other hospital for other reasons; 7) transferred to rehab/other hospital for chronic complications; 8) ordinary discharge + nurse assistance at home; 9) dismissal.

NYHA at follow-up: NYHA class will be assessed at hospital discharge, at 6 months, 1 year, yearly up to the 5th-year follow-up, and then yearly up to follow-up closure (10 years).

Date of events: during follow-up, the date of each possible event will be collected as “dd/mm/yyyy”

Follow-up death: death occurring after hospital-discharge. Further dichotomization into cardiovascular and all-cause mortality is based on VARC-2 criteria (38).

Follow-up stroke: any focal or global neurological syndrome occurring after discharge and caused by ischemia and/or haemorrhage not resolving within 24 hours. The diagnosis and nature of stroke will be made on the basis of findings from brain CT, or MRI, or based on the medical report of a consultant neurologist.

Follow-up myocardial infarction: any myocardial infarction occurring after discharge and requiring medical, interventional or surgical treatment occurring after discharge.

Follow-up re-intervention on the aortic valve: re-intervention is defined as any surgical or percutaneous interventional treatment that replaces (or repairs) an aortic prosthesis implanted at the time of the index procedure which is dysfunctional for either structural or non-structural reasons.

Follow-up aortic valve-related adverse event: this includes: 1) embolism; 2) valve thrombosis; 3) bleeding events; 3) structural valve deterioration; 4) paravalvular leakage; 5) operated valve endocarditis; 6) haemolysis, based on the definitions of current Guidelines for reporting mortality and morbidity after cardiac valve interventions (39).

Follow-up repeated revascularization: any CABG and/or PCI performed after discharge for coronary graft dysfunction and/or valve-related coronary complication. Any revascularization due

to the progression of an untreated subcritical (at the time of the index procedure) coronary target will not be considered.

Need for implantable cardioverter-defibrillator: collected as a dichotomous variable (yes/no)

Composite outcome: according to VARC-2 definitions (38), this includes: 1) device success (absence of procedural mortality with correct positioning of a single prosthesis and with intended performance of the prosthesis); 2) early safety at 30 days (composite endpoint of all-cause mortality, all strokes, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary obstruction requiring intervention, major vascular complication or valve-related dysfunction requiring repeat procedure); 3) clinical efficacy after 30 days (composite endpoint of all-cause mortality, all strokes, hospitalization for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV, valve related dysfunction); 4) time-related valve safety (composite endpoint of structural valve deterioration requiring repeat procedure, prosthetic valve endocarditis, thrombosis, thrombo-embolic events or valve-related VARC bleeding).

Follow-up MACCE: defined as a composite end-point occurring after the 30-day time-point (considered as hospitalization, 30th day if discharged home, or during “rehab-hospitalization” at any time point if never discharged home), and including any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, follow-up repeated revascularization

Assessment of post procedural aortic prostheses performance: data on valve and prosthetic performances will be recorded according to medical reports from a consultant echocardiographer. Data will be collected before surgery, before hospital discharge, at 30 days after surgery, 6 months, 1 year after implantation, yearly thereafter up to the follow-up closure (10th year). Data collected at echocardiographic examination are based on VARC-2 criteria (38), and aimed at exploring prosthetic valve-performance and ventricular performance. A minimum set of echocardiographic data will be considered, as follows: 1) left ventricular (LV) function (EF% based on Simpson’s method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and

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3 prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective
4 orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade
5 (defined as mild, moderate or severe based on several different echocardiographic indexes as
6 regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local
7 institutional policies). Further assessment of “intra-prosthetic”, “peri-prosthetic” or “combined
8 intra+peri-prosthetic” regurgitation will be added.
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11 *Short-Form 8 SF-8 Health Survey questionnaire:* will be based on eight questionnaire items
12 reported in Table 4 (52). This examination will be administered before surgery, at hospital
13 discharge, at 30-days, at 6 months, at 1 year, yearly thereafter up to the 5th-year of follow-up, then at
14 follow-up closure (10th year).
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27 **ETHICS AND DISSEMINATION**
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30 The study is approved by the local Institutional Review Boards/Ethical Committees, according to
31 local or national guidelines for approval of registry studies. Patient’s informed consent will be
32 always obtained.
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35 This multicenter, prospective open registry is designed with the aim of investigating a number of
36 controversial issues regarding current treatment-options and risk factors for the surgical therapy of
37 SAVS with or without CAD. Several studies and information are expected to derive from the data
38 collected in the registry. These data will provide further knowledge on the mechanisms leading to
39 adverse events during or after surgery for SAVS and help their prevention, thus allowing a
40 “tailored” surgical approach for the treatment of this disease.
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43 Several studies are planned at the moment:
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46 Primary study:
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49 1) A 5-year study comparing all-cause mortality between SAVR and surgical TAVR. We
50 expect to report a 10% superiority of SAVR vs. TAVR according to sample size calculation
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and literature data (7,36). This study will also report echocardiographic data, functional status, quality of life, incidence of cardiovascular mortality, reinterventions on the aortic valve, and incidence of structural valve deterioration between “all-comers” surgical TAVR and SAVR. The study is expected 6 years after the start of data collection and it is aimed at being presented in a major European cardiology journal

Secondary sub-studies

- 2) An observational study providing results of the different surgical techniques to treat SAVS - in terms of “all-cause” and “cardiovascular” mortality, major morbidity and VARC-2 follow-up outcome analysis - at the end of the 5th-year follow-up of the last patient enrolled. We aim at present this study in a major cardio-thoracic surgical Congress and publish it in a Congress-satellite Journal. This study is expected after 6 years from the start of data collection.
- 3) A study comparing early and 5-year follow-up outcome of mechanical vs. biological prostheses in young population (<70 years of age). Propensity-matching and risk-adjusted analyses will be performed. It is aimed at being presented in a major American journal of the cardiology field. This study is expected after 6 years from the start of data collection.
- 4) A study comparing early and 5-year follow-up outcome of stented vs. stentless vs. sutureless bioprostheses vs. surgical TAVR in small annuli (≤ 21 mm). Propensity-matching and risk-adjusted analyses will be performed. Post-hoc analysis will help elucidate between-group differences. It is aimed at being presented in a major European cardiology journal of the cardiology field. This study is expected after 6 years from the start of data collection.
- 5) A study comparing early and 5-year follow-up outcome of sutured (both stented and stentless) bioprostheses vs. sutureless bioprostheses. Propensity-matching and risk-adjusted analyses will be performed. It is aimed at being presented in a major American or European journal of the cardiology field. This study is expected after 6 years from the start of data collection.

- 6) A 5-year outcome study comparing SAVR vs. surgical TAVR in intermediate-risk patients. Propensity-matching and risk-adjusted analyses will be performed. This study is aimed at being presented in a major European journal of the cardiology field. It is expected after 6 years from the start of data collection.
- 7) A 3-year outcome study comparing different surgical techniques of TAVR (i.e. trans-apical vs. trans-aortic vs. trans-axillary approach). Propensity-matching and risk-adjusted analyses will be executed if baseline differences are identified between the 3 subpopulations. Post-hoc statistical analyses will identify outcome-differences between the 3 subgroups. This study is aimed at being presented in a European journal of the field. This study is expected after 4 years from the start of data collection.
- 8) A 5-year outcome study resembling the previous one for final outcome data. This study is aimed at being presented in a major American journal of the field . It is expected after 6 years from the start of data collection.
- 9) An interim-study analyzing 30-day outcome of the first 4000 patients enrolled. This study is expected after 1 year from the start of data collection. It is aimed at being presented in a major European cardio-thoracic Meeting and satellite journal.
- 10) A study analyzing 30-day outcome and 1-year follow-up outcome of the first 4000 SAVR-patients enrolled. Sub-group analyses will be aimed at compare different surgical accesses (i.e. sternotomy vs. mini-sternotomy vs. mini-thoracotomy). Propensity-matching, risk-adjusted and post-hoc analyses will be done appropriately to nullify potential bias in the interpretation of the results, and to compare the results of each surgical subgroup. This study is expected after 2 years from the start of data collection. It is aimed at being presented in a major European cardio-thoracic Congress and satellite journal
- 11) A study analyzing the 5-year outcome after SAVR+CABG vs. TAVR±PCI (regardless of the surgical access for SAVR and TAVR) in patients admitted with contemporary critical aortic stenosis and coronary disease. Propensity-score and risk-adjusted analyses will be

done as appropriate for a correct interpretation of data. Particular attention will be focused on the role of “incomplete revascularization” and of different techniques of “staged TAVR and PCI” in the transcatheter group. This study is expected after 6 years from the start of data collection. It is aimed at being presented in a major European cardio-thoracic Congress and satellite journal

12) A 10-year study comparing all-cause and cardiovascular mortality, echocardiographic data, functional status, quality of life, incidence of reinterventions on the aortic valve, and incidence of structural valve deterioration between SAVR and surgical TAVR. This study is expected after 11 years from the start of data collection and it is aimed at being presented in a major European cardiology journal

13) A 10-year study comparing all-cause and cardiovascular mortality, echocardiographic data, functional status, quality of life, incidence of reinterventions on the aortic valve and incidence of structural valve deterioration between SAVR with “sutured” valves and SAVR with “sutureless” valves. This study is expected after 11 years from the start of data collection and it is aimed at being presented in a major cardiology journal

Further studies aimed at peculiar sub-group analyses are not considered at this moment, but the E-AVR Steering Committee will evaluate any study/sub-study proposal from any researcher involved in the Registry, and accept/reject it by vote after review and discussion about its feasibility.

Therefore, research findings from the E-AVR registry will be disseminated among the scientific community. They will be presented at international congresses and published in peer reviewed international journals in the fields of cardiac surgery and cardiology. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship. Data collection, analysis and writing process will be monitored by the Steering Committee of the E-AVR, which is made up of the Principal Investigator and a local Representing Member from each of the participating centres. It is expected that periodical E-AVR

Steering Committee meetings will occur, every 6 months for the first 2 years, yearly thereafter up to the end of follow-up. A complete list of the E-AVR Collaborators is reported in Appendix. The Members of the Steering Committee will take responsibility for the quality of data through local audit.

Investigators will be eligible for authorship if they contribute substantially to study planning, data collection, data analysis and interpretation, writing and critical review of the manuscripts. Two authors per centre will be included as main authors of each study. As a member of the Steering Committee, the local Representing Member will take any decisions on co-authorship related to his/her centre on the basis of the above criteria. Those researchers who plan a sub-study, interpret the analysis and write the article will be the first and last authors of the study. Analyses will be performed and/or monitored by an independent Central Core Statistic Laboratory. When an article is submitted to a journal with a maximum number of co-authors, the Steering Committee will decide on the authors on the basis of their contribution to the design of the study, data collection, interpretation of data, writing, and critical review of the paper.

In the event of future merging with other contemporary registries (e.g. collecting data on concurrent interventional – i.e. percutaneous transfemoral, transcarotid or trans-axillary - TAVR procedures), the co-authorship of comparative studies (e.g. between surgical and interventional treatments) will be defined by the Steering Committees of the different registries involved. However, data will not be made available for sharing until after publication of the principal results of the study. Thereafter, anonymized individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements, and value for money. Anonymized data will be shared as long as the patient has agreed and consented to this. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research.

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COMPETING INTEREST STATEMENT

None to declare.

FIGURE LEGENDS

Figure 1. Flowchart of enrolment criteria and surgical techniques considered in the registry (CAD: coronary artery disease)

Figure 2. Flowchart of time-points for data collection

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M.D., Vasilis Babaliaros, M.D., Wilson Y. Szeto, M.D., Mathew R. Williams, M.D., Dean Kereiakes, M.D., Alan Zajarias, M.D., Kevin L. Greason, M.D., Brian K. Whisenant, M.D., Robert W. Hodson, M.D., Jeffrey W. Moses, M.D., Alfredo Trento, M.D., David L. Brown, M.D., William F. Fearon, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Wael A. Jaber, M.D., William N. Anderson, Ph.D., Maria C. Alu, M.M., and John G. Webb, M.D., for the PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2016;374:1609-20.

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AUTHOR’S CONTRIBUTIONS:

F. Onorati: Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

R. Gherli: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

G. Mariscalco: Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

E. Girdauskas: Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

E.O. Quintana: Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

F. Santini: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

M. De Feo: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

S. Sponga: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

P. Tozzi: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

M. Bashir: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

A. Perrotti: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

A. Pappalardo: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

V.G. Ruggieri: Conception of the study, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

G. Santarpino: drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspects of the study

M. Rinaldi: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

Silva RRG: Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing

F. Nicolini: Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing

TABLE 1: Stages of renal failure.

Stages	eGFR level (mL/min/1.73 m2)
1	90 or above
2	89 to 60
3a	59 to 44
3b	44 to 30
4	29 to 15
5	Less than 15 or on dialysis

TABLE 2: New York Heart Association functional classes.

<i>Class</i>	<i>Definition</i>
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest
IV	Severe limitations. Experiences symptoms even while <i>at rest</i> . Mostly bedbound patients

TABLE 3: Definition criteria of type V myocardial infarction.

Baseline condition	Definition
1. In patients with normal baseline CK-MB or cTn (I or T)	The peak CK-MB measured within 48 hours of the procedure rises to $\geq 10 \times$ the local laboratory upper limit of normal (ULN), or to $\geq 5 \times$ ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the procedure rises to $\geq 70 \times$ the local laboratory ULN, or $\geq 35 \times$ ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB.
2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Table 4: SF-8TM Health Survey

Date _____ Name _____

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. For each of the following questions, please mark an [x] in the one box that best describes your answer.

I. Overall, how would you rate your health during the past 4 weeks?

Excellent Very Good Good Fair Poor Very Poor

II. During the past 4 weeks, how much did physical health problems limit your physical activities (such as walking or climbing stairs)?

Not at all Very little Somewhat Quite a lot Could not do physical activities

III. During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?

Not at all Very little Somewhat Quite a lot Could not do daily work

IV. How much bodily pain have you had during the past 4 weeks?

None Very mild Mild Moderate Severe Very severe

V. During the past 4 weeks, how much energy did you have?

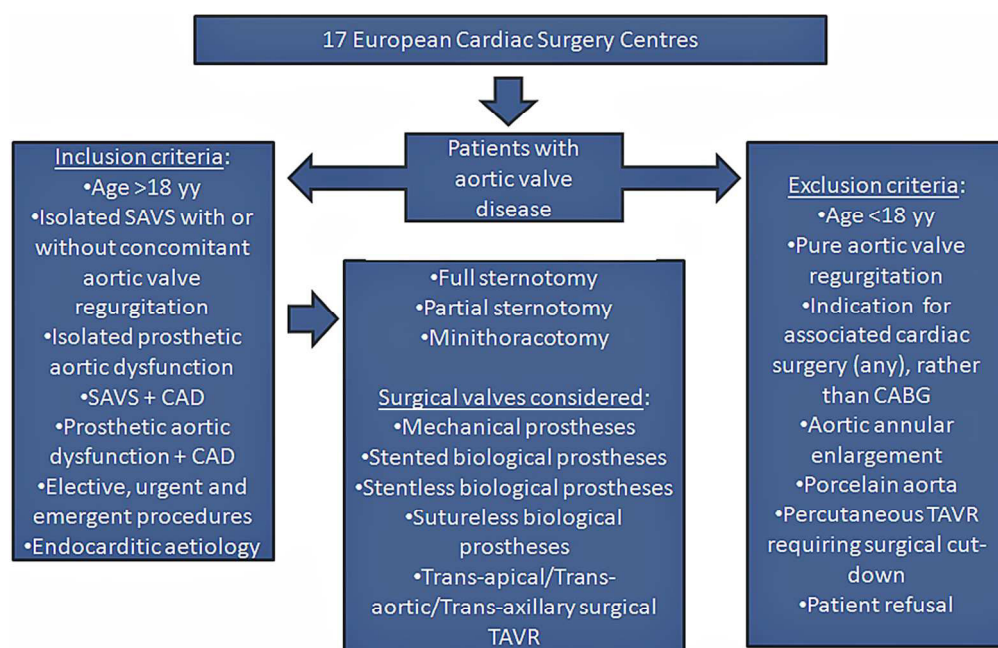
Very much Quite a lot Some A little None

VI. During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?

Not at all Very little Somewhat Quite a lot Could not do social activities

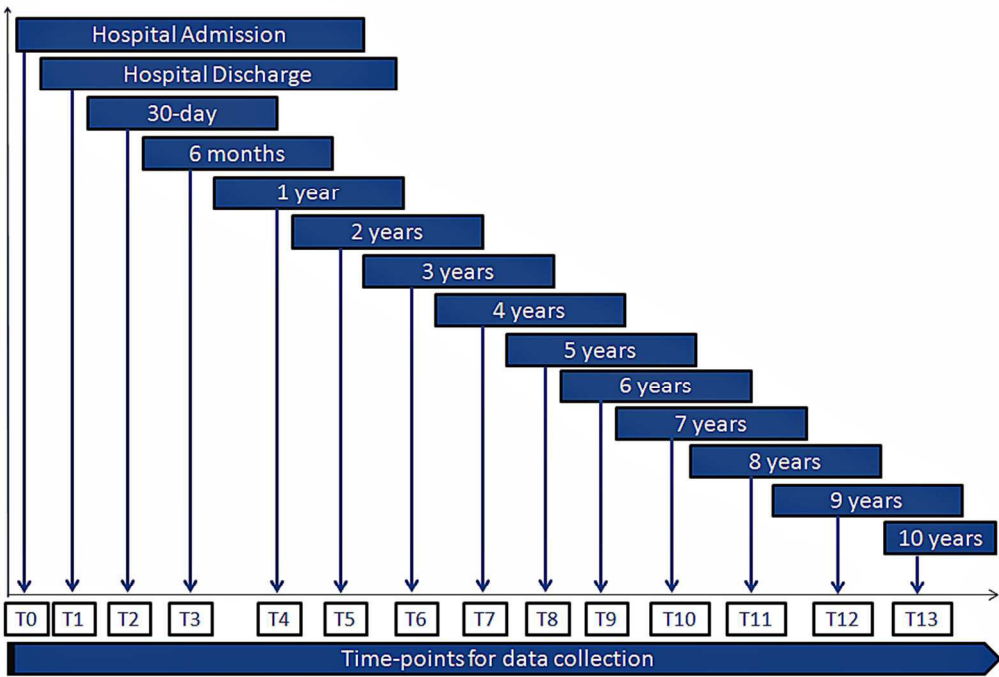
VII. During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?

1
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3 Not at all Slightly Moderately Quite a lot Extremely
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5 VIII. During the past 4 weeks, how much did personal or emotional problems keep you from
6
7 doing your usual work, school or other daily activities?
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9 Not at all Very little Somewhat Quite a lot Could not do daily activities
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Flowchart of enrolment criteria and surgical techniques considered in the registry (CAD: coronary artery disease)

81x56mm (300 x 300 DPI)



Flowchart of time-points for data collection

81x56mm (300 x 300 DPI)

Appendix. E-AVR Collaborators

1. **Tiziano Gherli, MD** – Div. Cardiac Surgery, University of Parma, Parma, Italy
2. **Giuseppe Faggian, MD** and **Livio San Biagio, MD** – Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy
3. **Aung Oo, MD PhD** and **Rakesh Uppal, MD PhD** - Division of Cardiac Surgery, St. Barth Hospital NHS, London, UK
4. **Francesco Musumeci, MD** – Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy
5. **Hermann Reichenspurner, MD** – Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany
6. **Manuel Castellà, MD** – University Hospital Clinic, Barcellona, Spain
7. **Antonio Salsano, MD** – Cardiac Surgery Unit, University of Genova, Genoa, Italy
8. **Alessandro Della Corte, MD PhD** and **Ciro Bancone, MD** - Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy
9. **Ugolino Livi, MD** - Cardiothoracic Department, University Hospital of Udine, Udine, Italy
10. **Nicola Masala, MD** and **Gavin J. Murphy, MD** - Department of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK
11. **Sidney Chocron, MD PhD** - Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France
12. **Giuseppe Gatti, MD** and **Luca Maschietto, MD** - Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy
13. **Stefano Salizzoni, MD** – Dpt of Cardiac Surgery, Torino University Hospitals, Turin, Italy
14. **Francesco Pollari, MD** - Cardiovascular Center, Klinikum Nürnberg – Paracelsus Medical University, Nuremberg, Germany

15. **Alessandro Di Cesare, MD** - Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN,
Hopital Robert Debre', Reims, France

16. **Giulia Bisoffi, PhD**, Unit for Clinical Research and Biostatistics, Verona University
Hospital, Verona, Italy

For peer review only

SPIRIT CHECKLIST

1. Outcomes comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)
2.
 - a. ClinicalTrials.gov # NCT03143361
 - b. WHO Dataset specifications:
 - i. European Aortic Valve Registry (E-AVR); protocol n. 1
 - ii. Registration date: May 3, 2017
 - iii. ClinicalTrials.gov # NCT03143361
 - iv. Fundings: none
 - v. University of Parma, Parma, Italy
 - vi. None
 - vii. Prof. Francesco Nicolini, Div. Cardiac Surgery, University of Parma, Parma, Italy; email: francesco.nicolini@unipr.it; Via A. Gramsci 14 – 43126 - Parma (PR) – Italy
 - viii. Prof. Francesco Nicolini, Div. Cardiac Surgery, University of Parma, Parma, Italy; email: francesco.nicolini@unipr.it; Via A. Gramsci 14 – 43126 - Parma (PR) – Italy
 - ix. Dr. Francesco Onorati, Div. Cardiac Surgery, University Hospitals in Verona, Verona, Italy; email: francesco.onorati@aovr.veneto.it; Piazzale Stefani, 1 – 37100 - Verona (VR) – Italy
 - x. European Aortic Valve Surgery Registry
 - xi. Outcome comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)
 - xii. Italy, United Kingdom, France, Germany, Spain, Switzerland
 - xiii. Surgical treatment of aortic valve stenosis with or without concomitant coronary artery disease
 - xiv. The following interventions will be analyzed:
 1. Surgical Aortic Valve Replacement (SAVR) via:
 - a. Full Sternotomy
 - b. Mini-thoracotomy
 - c. Mini-sternotomy
 - d. Stented prostheses (mechanical and biological)
 - e. Stentless prostheses (biological)
 - f. Sutureless prostheses (biological)
 2. Surgical Transcatheter Aortic Valve Replacement (TAVR) via:
 - a. Mini-thoracotomy via trans-apical route
 - b. Mini-sternotomy via trans-aortic route
 - c. Mini-thoracotomy via trans-aortic route
 - d. Sub-clavear via trans-axillary route
 - xv. Inclusion criteria: Isolated severe aortic valve stenosis (SAVS) with or without concomitant aortic valve regurgitation; isolated prosthetic aortic dysfunction; SAVS + coronary artery disease (CAD); prosthetic aortic dysfunction + CAD; age >18 yy; elective, urgent and emergent procedures; endocarditic aetiology; exclusion criteria: concomitant mitral valve surgery, tricuspid valve surgery, aortic surgery, atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG); surgical aortic annular enlargement; porcelain aorta; pure aortic valve regurgitation; percutaneous TAVR requiring surgical cut-down; patient refusal
 - xvi. Prospective non-randomized open cohort study
 - xvii. 1st November, 2017
 - xviii. A minimum of 8000 patients in 2 years of enrolment
 - xix. Waiting for the start of enrolment
 - xx. All-cause mortality (any death, either of cardiovascular and non cardiovascular nature) at 5 year from enrolment. Checked by linking with regional Social Security

Death and Events Master files, by phone contact with general practitioner, and in case of absent/missing data by direct phone contact with families.

xxi.

1. *All-cause mortality* (any death, either of cardiovascular and non cardiovascular nature) at 30-day, 6-month, 1-year and yearly up to 10-year (5-year excluded) follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with families.
2. *Cardiovascular mortality* (the sum of: 1) death due to proximate cardiac cause, e.g. myocardial infarction, cardiac tamponade, worsening heart failure, low cardiac output syndrome, etc.; 2) death caused by non-coronary vascular conditions, e.g. pulmonary embolisms, stroke, aortic rupture or vascular dissection, etc; 3) all procedure-related deaths, including those related to a complication of the procedure or a treatment for a complication of the procedure; 4) all valve-related deaths including valve dysfunction - structural or non-structural - and other valve-related adverse events; 5) sudden or unwitnessed death) at 30-day, 6-month, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with families.
3. *30-day Type 5 myocardial infarction*: defined according to the recent criteria defined by Moussa et al. (J Am Coll Cardiol 2013; 62:1563-1570). Assessed at 30-day. Collected from hospital registries.
4. *30-day stroke*: classified as 1) ischemic; 2) haemorrhagic; 3) unknown, according to VARC-2 consensus (Eur J Cardio Thorac Surg 2012; 42: S45–S60). The diagnosis and nature of stroke will be supported by CT or MRI imaging and confirmed by a consultant neurologist. Assessed at 30-day. Collected from hospital registries.
5. *Early repeated intervention for index intervention failure*: This refers to any surgical or percutaneous procedure on the aortic valve and/or the coronary arteries, performed during the same hospital stay for any prosthesis-related or graft-related complication. These events will be marked as occurring or not, and further detailed in their nature (“valvular early procedure”, “coronary early procedure” or “coronary + valvular early procedure”). Further details will be collected as explanatory notes. Assessed at 30-day. Collected from hospital registries.
6. *Postoperative need for prolonged use of inotropes*: this refers to the use of inotropes for >72 hours after the index operation. The type, dose and duration of administered inotropes will be also collected. Assessed at 30-day. Collected from hospital registries.
7. *Need for intra-aortic balloon pump (IABP)*: intra- or postoperative insertion of an intra-aortic balloon pump device. Assessed at 30-day. Collected from hospital registries.
8. *Need for extracorporeal mechanical oxygenation (ECMO)*: intra- or postoperative insertion of an extracorporeal mechanical pump/oxygenation device. Assessed at 30-day. Collected from hospital registries.
9. *Surgical site infection*: wound complications are graded according to the Centre for Disease Control and Prevention definitions of surgical site infections (Infect Control Hosp Epidemiol 1999; 20: 250-278). Any surgical site infection occurring within three months after surgery will be considered as a postoperative wound infection. Assessed at 30-day and 3 months after procedure. Collected from hospital registries and outpatient clinic registries.
10. *Bleeding*: classified as 1) life-threatening or disabling bleeding; 2) major bleeding; 3) minor bleeding, according to the recent definition criteria

- reported by the VARC-2 document (Eur J Cardio Thorac Surg 2012; 42: S45–S60). Assessed at 30-day. Collected from hospital registries.
11. *Blood losses at 12 hours*: the amount of postoperative blood losses from mediastinal drainages 12 hours after surgery. Intraoperative blood losses are not taken into account. Nadir haemoglobin and nadir haematocrit will be collected. Assessed at 30-day. Collected from hospital registries.
 12. *Use of blood products during hospitalization for the index surgical procedure*: total amount of blood products (detailed as red packed cells, fresh frozen plasma, or platelet concentrates) from the beginning of surgery to the day of discharge. Assessed at 30-day. Collected from hospital registries.
 13. *Resternotomy for bleeding*: Any reoperation for postoperative bleeding, regardless of concomitant hemodynamic problems. Assessed at 30-day. Collected from hospital registries.
 14. *Pericardial effusion requiring treatment*: any pericardial effusion requiring interventional treatment (e.g. pericardiocentesis, subxifoid drainage, resternotomy, etc) due to cardiac tamponade, sub-tamponade, or hemodynamic instability refractory to conservative treatment-strategies. Assessed at 30-day. Collected from hospital registries.
 15. *Acute renal failure*: severity of acute renal failure after surgery will be graded in AKIN stages from 1 to 3, according to VARC-2 criteria (Eur J Cardio Thorac Surg 2012; 42: S45–S60). Assessed at 30-day. Collected from hospital registries.
 16. *Atrial fibrillation*: any new paroxysmal/permanent atrial fibrillation episode requiring or not requiring pharmacological or electrical cardioversion attempts. Number of recurrences will be also collected. Assessed at 30-day. Collected from hospital registries.
 17. *Cardiac conduction disturbances*: defined as a new left bundle branch block, right bundle branch block, or AV-block (1st, 2nd or 3rd degree). Diagnosis will be based on official medical reports from a consultant cardiologist. In case of progressive bradi-arrhythmias, the evolution of the arrhythmias will be collected. Assessed at 30-day. Collected from hospital registries.
 18. *Need for permanent PMK*: collected as a dichotomic variable. Type of permanent pacing set-up (e.g. AAI, VVI, DDD, etc) will be collected. Assessed at 30-day. Collected from hospital registries.
 19. *Length of stay in the intensive care unit*: number of hours spent in the intensive care unit from surgery. Readmissions to intensive care unit will be considered and included in the number estimation. Assessed at 30-day. Collected from hospital registries.
 20. *Length of in-hospital stay*: number of days spent into hospital (ICU-stay will be added) from the day of surgery to hospital discharge to any other hospital ward, rehabilitation unit or home. Assessed at 30-day. Collected from hospital registries.
 21. *Follow-up stroke*: any focal or global neurological syndrome occurring after discharge and caused by ischemia and/or haemorrhage not resolving within 24 hours. The diagnosis and nature of stroke will be made on the basis of findings from brain CT, or MRI, or based on the medical report of a consultant neurologist. Assessed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
 22. *Follow-up myocardial infarction*: any myocardial infarction occurring after discharge and requiring medical, interventional or surgical treatment occurring after discharge. Assessed at 6-months, 1-year and yearly up to 10-

- year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
23. *Follow-up re-intervention on the aortic valve*: re-intervention is defined as any surgical or percutaneous interventional treatment that replaces (or repairs) an aortic prosthesis implanted at the time of the index procedure which is dysfunctional for either structural or non-structural reasons. Analyzed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
24. *Follow-up aortic valve-related adverse event*: this includes: 1) embolism; 2) valve thrombosis; 3) bleeding events; 3) structural valve deterioration; 4) paravalvular leakage; 5) operated valve endocarditis; 6) haemolysis, based on the definitions of current Guidelines for reporting mortality and morbidity after cardiac valve interventions (J Thorac Cardiovasc Surg 2008; 135: 732-8). Analyzed at 30-days, 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
25. *Follow-up repeated revascularization*: any CABG and/or PCI performed after discharge for coronary graft dysfunction and/or valve-related coronary complication. Any revascularization due to the progression of an untreated subcritical (at the time of the index procedure) coronary target will not be considered. Analyzed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
26. *Composite outcome*: according to VARC-2 definitions (Eur J Cardio Thorac Surg 2012; 42: S45–S60), this includes: 1) device success (absence of procedural mortality with correct positioning of a single prosthesis and with intended performance of the prosthesis); 2) early safety at 30 days (composite endpoint of all-cause mortality, all strokes, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary obstruction requiring intervention, major vascular complication or valve-related dysfunction requiring repeat procedure); 3) clinical efficacy after 30 days (composite endpoint of all-cause mortality, all strokes, hospitalization for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV, valve related dysfunction); 4) time-related valve safety (composite endpoint of structural valve deterioration requiring repeat procedure, prosthetic valve endocarditis, thrombosis, thrombo-embolic events or valve-related VARC bleeding). Analyzed at 30-days, 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
27. *MACCE* (defined as composite end-point including any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, repeated revascularization) at 30-day, 6-month, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master

files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with families.

28. Quality of life (QoL; defined according to Short Form-8 questionnaire) at hospital admission, at 30-day, 6-months, 1-year and yearly up to 10-year follow-up. QoL will be assessed during follow-up visits at outpatient clinics or, if other methods are not possible, by telephone interview.

29. Echocardiographic data of prosthesis performance. Data collected at echocardiographic examination are based on VARC-2 criteria (37). A minimum set of echocardiographic data will be considered: 1) left ventricular (LV) function (EF% based on Simpson's method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade (defined as mild, moderate or severe based on several different echocardiographic indexes as regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local institutional policies). Further assessment of "intra-prosthetic", "peri-prosthetic" or "combined intra+peri-prosthetic" regurgitation will be added.

Echocardiographic data will be assessed at hospital admission, before hospital discharge, at 30 days after surgery, 6 months, 1 year after implantation, and yearly thereafter up to the follow-up closure (10th year) by Institutional 3rd level certified Echocardiographic Laboratories: 5% of these echocardiographic exams will be reviewed centrally (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) by third level certified echocardiographers.

3. Protocol n.1.2.17 of 12th August, 2017

4. Funding: None

- 5.

- a. *Francesco Nicolini, MD PhD, Associate Professor*. Div. Cardiac Surgery, University of Parma, Parma, Italy; Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing, member of the E-AVR Steering Committee

Francesco Onorati, MD PhD. Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Riccardo Gherli, MD. Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Giovanni Mariscalco, MD PhD. Dpt. of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK; Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Evaldas Girdauskas, MD. Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany, Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Eduardo Obrador Quintana, MD. University Hospital Clinic, Barcellona, Spain; Design of the study, drafting the paper, critically revising the paper, final approval of the version to be

published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Francesco Santini, MD Full Professor. Cardiac Surgery Unit, University of Genova, Genoa, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Marisa De Feo, MD PhD Full Professor. Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Sandro Sponga, MD PhD. Cardiothoracic Department, University Hospital of Udine, Udine, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Piergiorgio Tozzi, MD Associate Professor. Cardiac Surgery Unit, Centre Hopitalier Universitaire Vaudois, Lausanne Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Mohammad Bashir, MD. Division of Cardiac Surgery, St. Barth Hospital NHS, London, UK. Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Andrea Perrotti, MD. Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France. Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Aniello Pappalardo, MD. Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy. Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Vito Giovanni Ruggieri, MD Professor. Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN, Hopital Robert Debre', Reims, France; Conception of the study, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Giuseppe Santarpino, MD. Cardiovascular Center, Klinikum Nürnberg – Paracelsus Medical University, Nuremberg, Germany. Drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspects of the study, member of the E-AVR Steering Committee

Mauro Rinaldi, MD PhD Full Professor. Department of Cardiac Surgery, Torino University Hospitals, Turin, Italy. Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Carlo Antona, MD Full Professor. Department of Cardiac Surgery, Ospedale Sacco, Milan, Italy; Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee.

Silva Ronaldo Rouvher Guedes, PhD, Biostatistician. Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy. Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing

Tiziano Gherli, MD Full Professor. Div. Cardiac Surgery, University of Parma, Parma, Italy; Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be

accountable for all aspect of the study, ClinicalTrials.gov publishing, member of the E-AVR Steering Committee

Giuseppe Faggian, MD PhD Full Professor. Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; Conception of the study, design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee.

- b. Prof. Francesco Nicolini, Div. Cardiac Surgery, University of Parma, Parma, Italy; email: francesco.nicolini@unipr.it; Via dell'Università n.12 – 43121 - Parma (PR) – Italy.
- c. Funders: None. Sponsor roles: no external sponsor for the trial. The PI (Prof. F. Nicolini) has active participation in study design, collection and management of data (analysis of data performed by an external Statistical Core Laboratory), interpretation of data, writing reports, and decision to submit the reports for publication; however, no ultimate Authority over any of these activities
- d. Coordinating Centre composition: Professor Francesco Nicolini, MD, and Professor Tiziano Gherli, MD; Div. Cardiac Surgery University of Parma. Roles: coordination of the Registry, active participation in study design, collection and management of data (analysis of data performed by an external Statistical Core Laboratory), interpretation of data, writing reports, and decision to submit the reports for publication. No ultimate Authority over any of these activities. Responsibility: coordination of the Registry, E-AVR Steering Committee adherence to its roles.
Steering Committee: Composition: F. Onorati, F. Nicolini, R. Gherli, G. Mariscalco, E. Girdauskas, E.O. Quintana, F. Santini, M. De Feo, S. Sponga, P. Tozzi, M. Bashir, A. Perrotti, A. Pappalardo, V.G. Ruggieri, G. Santarpino, M. Rinaldi, C. Antona, Silva RRG, T. Gherli, G. Faggian.
Roles: Generate the sequence to maintain anonymized the entire set of data, protect confidentiality about patient identity before, during and after the trial, and retain data in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.
Take responsibility of data collection, data monitoring through local auditing, endpoint analysis, and writing process; evaluation of sub-study proposal from researchers involved in the Registry, and accept/reject it by vote after review and discussion about its feasibility; take any decisions on co-authorship on the basis of individual contribution to the design of the study, data collection, interpretation of data, writing, and critical review of the paper; establish periodical E-AVR Steering Committee meetings; maintain a copy of the complete database.
Take responsibility of further checking, reviewing, correcting and merging in case of incomplete or contradictory data, and in case of data without identification code.
Data Management: apart from a local data auditing (responsibility of the E-AVR Steering Committee), the Central Core Statistical Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) will centrally adjudicate clinical outcome data, and take responsibility of storage, analysis and auditing of data every six-months. Furthermore, 5% of echocardiographic data will be reviewed centrally (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) by third level certified echocardiographers

6.

- a. The prevalence of severe aortic valve stenosis (SAVS) correlates with age, and its treatment is expected to increase parallel to the improved life-expectancy reported in Western Countries (1-2). Traditional surgical aortic valve replacement (SAVR) has been the gold standard of treatment for decades, with well-documented benefits in terms of symptom improvement and survival (3-4). Recent technological advances allowed interventional and surgical transcatheter aortic valve replacements (TAVR), which proved to be effective alternatives to traditional SAVR, in both high-risk and intermediate-risk patients (5-12). Therefore, SAVR and TAVR represent nowadays the standard surgical armamentarium for aortic valve replacement. Alternative surgical approaches, based on the concept of TAVR (13,14), have in fact been developed. There are on the market two types of “sutureless”

valves (i.e. Sorin Perceval and Edwards Intuity) at the moment - aimed at reducing some surgical drawbacks such as cross-clamp time and myocardial ischemia-reperfusion injury (13,15-20) – but it is possible that new “sutureless” valves will enter the market in the next future. Moreover, different mini-thoracotomy and mini-sternotomy approaches to SAVR have been widely adopted by the surgical community - with both “sutured” and “sutureless” valves - in order to reduce surgical trauma, systemic inflammatory response, and major organ morbidity (13,15,16). Various different combinations of minimally invasive accesses and the use of last-generation valves have been reported to date (14,17,18). But despite early enthusiasm about preliminary results with these technological improvements, none of these techniques has yet replaced traditional SAVR in standard surgical practice, mainly because reporting of results of these alternative techniques tends to be biased by single-centre design, limited sample-size, and the strict inclusion/exclusion criteria of the published studies (13,14).

Another “hot topic” in this debate relates to valve durability, given that the long-term durability of both TAVR and sutureless valves is as yet unknown. Indeed, standard “sutured” surgical valves demonstrated excellent durability, both in the very-long term and in very-young adults below the 65-year cut-off age (21-23), which is still the threshold for biological valves recommended by European Society of Cardiology (ESC) / European Association for CardioThoracic Surgery (EACTS) guidelines (24). This issue is of particular interest, given that the use of TAVR has increased in younger intermediate-risk patients, despite recent caveats relating to early degeneration of TAVR (25,26).

Similarly, improved life-expectancy has led to a growing number of patients with degenerated dysfunctioning aortic bioprostheses requiring surgical treatment. Again, surgical aortic prosthetic replacement (SAPR) has been traditionally considered the only treatment strategy for these patients, given the excellent results, recently confirmed by several studies (27,28). Again, transcatheter treatments (“valve-in-valve”) have recently demonstrated comparable or sometimes superior results in redo-scenarios (29). Therefore, data on the efficacy, safety and durability of these technological improvements are essential for providing “strong” statements in future guidelines, and for evaluating the extension of these techniques to low-risk and young patients in the future.

Finally, it is well known that critical coronary artery disease (CAD) often coexists with SAVS. Although the standard treatment option for these patients has traditionally been SAVR plus coronary artery bypass grafting (CABG), the introduction of TAVR and minimally invasive surgical alternatives has considerably changed the available options, paving the way to combined less-invasive SAVR+CABG and/or TAVR±PCI (either before, during or after the surgical procedure) (30-34). Again, there is a great deal of confusion on the topic, and there are unanswered questions on the efficacy and safety of these options, as well as on what to expect from late follow-up when compared to the standard practice of SAVR+CABG.

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- b. Robust early and follow-up data on the safety and efficacy of surgical TAVR, last-generation sutureless surgical valves, and minimally-invasive approaches compared with standard SAVR, with or without a contemporary (surgical or interventional) treatment of concurrent CAD, are still lacking for a real-world large population of patients at variable surgical risk. Such data is urgently required for the correct allocation of therapy in daily surgical practice. Furthermore, data on quality of life and functional echocardiographic results with different surgical alternatives might similarly help physicians in decision-making in local "Heart Teams". Data from a multicentre, real-world, open registry enrolling all patients with SAVS±CAD consecutively referred to several Centres at different European latitudes should help to answer some of these open questions.
In particular, comparative analyses between mid-to-long term outcome of SAVR vs surgical TAVR will clarify the mid-to-long term prognosis associated with these 2 different techniques (risk of death, risk of reintervention, functional class, quality of life, etc)
Comparison between sutured and sutureless aortic prostheses, since hospitalization to 10-year follow-up, will elucidate if (and how much) the use of rapid-deployment valves is superior compared to standard techniques
Comparisons of minimally invasive approaches and full-sternotomy, since hospitalization to 10-year follow-up, will define the safety and efficacy of the former over the latter techniques.
7. The principal objective of the study is the 5-year comparison between outcome after SAVR and outcome after surgical TAVR: we hypothesize to report a 10% superiority in terms of all-cause mortality in favor of SAVR vs. TAVR.
8. The trial is a prospective registry-based observational cohort study, enrolling all patients fulfilling inclusion criteria (all comers), aimed at a superiority design (10% superiority of SAVR vs. TAVR in 5-year all-cause mortality)

9. Settings: University hospitals and 3rd level community hospitals (France, Germany, Italy, Spain, Switzerland, United Kingdom).
10. Inclusion criteria: Isolated severe aortic valve stenosis (SAVS) with or without concomitant aortic valve regurgitation; isolated prosthetic aortic dysfunction; SAVS + coronary artery disease (CAD); prosthetic aortic dysfunction + CAD; age >18 yy; elective, urgent and emergent procedures; endocarditic aetiology. Exclusion criteria: concomitant mitral valve surgery, tricuspid valve surgery, aortic surgery, atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG); surgical aortic annular enlargement; porcelain aorta; pure aortic valve regurgitation; percutaneous TAVR requiring surgical cut-down; patient refusal.
Individuals who will perform the interventions: surgeons
- 11.
- a.
- Surgical aortic valve replacement (SAVR) with any of the following surgical accesses:
- i. Full sternotomy
 - ii. Mini-thoracotomy
 - iii. Mini-sternotomy
- And with any of the following prostheses:
- i. Mechanical prostheses
 - ii. Biological stented prostheses
 - iii. Biological stentless prostheses
 - iv. Biological sutureless prostheses
- OR
- Surgical Transcatheter valve replacement (TAVR) with any of the following surgical accesses:
- iv. Mini-thoracotomy via trans-apical route
 - v. Mini-sternotomy via trans-aortic route
 - vi. Mini-thoracotomy via trans-aortic route
 - vii. Sub-clavear via trans-axillary route
- SAVR will be performed always under cardiopulmonary bypass. TAVR will be administered on the beating heart or, rarely, under cardiopulmonary bypass or extracorporeal circulation and membrane oxygenation according to the clinical scenario and Heart Team choice (e.g. severe hemodynamic compromise avoiding the possibility to perform TAVR with a standard unassisted beating heart technique). All these strategies are administered the day scheduled for surgical intervention.
- b. Criteria for discontinuing, withdrawing or modifying allocated intervention: intraoperative demonstration of unexpected porcelain aorta; unplanned need for concomitant mitral valve surgery, and/or tricuspid valve surgery, and/or aortic surgery, and/or atrial fibrillation surgery, and/or any other associated cardiac surgical procedure (with the exception of CABG); unplanned need for a surgical aortic annular enlargement
- c. N.A.: there are no strategies to improve adherence to protocols: this because any intraoperative and postoperative strategy/protocol is allowed (observational nature of the study), and then recorded in the Registry.
- d. Concomitant interventions that are prohibited during the trial are: planned concomitant mitral valve surgery, tricuspid valve surgery, aortic surgery, atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG); planned surgical aortic annular enlargement.
Given the observational nature of this prospective registry-based cohort study, all the possible concomitant medical strategies of the daily care are allowed and reported in the registry.
12. Primary outcome:
- i. *5-year all-cause mortality* (time to event; proportion; 5-year time-point)
- Secondary outcomes:
- ii. *Cardiovascular mortality* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
 - iii. *All-cause mortality* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)

- iv. *Type 5 myocardial infarction* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- v. *Stroke* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- vi. *Early repeated intervention for index intervention failure* (time to event; proportion; 30-day).
- vii. *Postoperative need for prolonged use of inotropes* (final value; proportion; 30-day time-point)
- viii. *Need for intra-aortic balloon pump* (time to event; proportion; 30-day time-point)
- ix. *Need for extracorporeal mechanical oxygenation* (time to event; proportion; 30-day time-point)
- x. *Surgical site infection* (time to event; proportion; 30-day and 6-month time-points)
- xi. *Bleeding* (final value; proportion; 30-day time-point)
- xii. *Blood losses at 12 hours* (final value; proportion; 30-day time-point)
- xiii. *Use of blood products during hospitalization for the index surgical procedure* (final value; proportion; 30-day time-point)
- xiv. *Resternotomy for bleeding* (time to event; proportion; 30-day time-point)
- xv. *Pericardial effusion requiring treatment* (time to event; proportion; 30-day time-point)
- xvi. *Acute renal failure* (time to event; proportion; 30-day time-point)
- xvii. *Atrial fibrillation* (time to event and final value; proportion; 30-day time-point)
- xviii. *Cardiac conduction disturbances* (time to event; proportion; 30-day time-point)
- xix. *Need for permanent PMK* (time to event; proportion; 30-day time-point)
- xx. *Length of stay in the intensive care unit* (final value; proportion; 30-day time-point)
- xxi. *Length of in-hospital stay* (final value; proportion; 30-day time-point)
- xxii. *Follow-up re-intervention on the aortic valve*: (time to event; proportion; 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxiii. *Follow-up aortic valve-related adverse event* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point).
- xxiv. *Follow-up repeated revascularization* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxv. *Device success* (time to event; proportion; 30-day)
- xxvi. *Early safety at 30 days* ((time to event; proportion; 30-day)
- xxvii. *Clinical efficacy after 30 days* (time to event; proportion; 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxviii. *Time-related valve safety* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxix. *MACCE* (time to event; proportion; 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxx. *Quality of life* (change from baseline; median; hospital discharge, 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxxi. *Echocardiographic data of prosthesis performance* (change from baseline; median; hospital discharge, 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)

13. 2- year of enrolment, starting on November, 1st 2017 and ending on October 30th 2019; 10-year of follow-up (closure on September 30th 2029). Data collection pertaining the hospital course. Follow-up time points: 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year.

Hospital admission	Hospital course	Discharge	30-day	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8 year	9 year	10 year
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Enrollment Baseline data Quality of life (QoF) Echocardiographic parameters (Echo)	Data pertaining surgery and postoperative care. Hospital outcome adjudication	Type of discharge QoF Echo	Outcomes adjudication (O.A.) QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	Primary outcome O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo
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14. A minimum of 8000 patients enrolled over 2 years. The primary aim of the study is a 5-year comparison between SAVR and surgical TAVR: the sample size calculation is based on a recent published study (36), specifically on the 5-year all-cause mortality rate (24.6%) of the 620 intermediate risk patients, our target population, who underwent SAVR. We hypothesize that the 5-year mortality rate following SAVR is 10% inferior compared to the surgical TAVR, and calculate the sample size using a conservative one-sided log-rank test. Assuming that patients will enter the study uniformly over the 2 years accrual time, 5 years total follow-up time, 80% statistical power, 5% significance level and 1.5% (historical data) probability of patient’s right censoring occurs. The resulting sample size is 6493 subjects (3246 in the control group and 3247 in the treatment group). Therefore the expected number of 8000 patients over a 2-year enrolment period is far beyond the requested sample size of the primary endpoint of the trial.
15. This is an all-comers registry-based cohort study. Historical data from the participating Centres demonstrate that at least 8000 patients (far beyond the number requested by sample size calculation) will be collected in 2 years, using an “all-comers” strategy
16. N.A.
17. N.A.
- 18.
- a. Data will be prospectively collected in a dedicated Database. Data pertaining hospitalization will be collected by hospital registries, whereas variables and outcome events occurring after the index hospital discharge will be collected from outpatient clinics at the individual Institutions, and linking with regional Social Security Death and Events Master files. Events and outcome variables will be adjudicated centrally by a Central Core Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy). In the event of controversy on outcome adjudication, the outcome will be adjudicated after a final consult between the Central Core Laboratory and the E-AVR Steering Committee. Collection of data is under the responsibility of the Steering Committee local member at each participating Centre.
- Data will be audited from the Central Core Laboratory on a regular basis, as reported previously. In case of absent/missing data, variables and events will be collected by direct phone contact with general practitioners, and only if persistently missed by phone contact with patients and families.
- The Local E-AVR Steering Committee member is responsible for a continuous active auditing of local data. The Central Core Statistical Lab will perform 6-month external auditing by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator and E-AVR Steering Committee for further data checking and merging. Incomplete or contradictory data with patient identification code will be sent from Central Core Statistical Lab to the E-AVR Steering Committee local member for further data checking, review, correction and merging.

Laboratory parameters: baseline levels of haemoglobin, haematocrit, platelets, blood glucose, HbA1c, C-reactive protein, TT-INR, creatinine, e-GFR and albumin will be collected.

Units of measurement: Laboratory data will be collected according to fixed units of measurement in order to avoid any problem stemming from differences in units used by the various participating centres, during data merging and analysis. The fixed units of measurement are reported in the dedicated CRF datasheet.

Short-Form 8 SF-8 Health Survey questionnaire: will be based on eight questionnaire items reported in Table 4 of the protocol.

Echocardiographic data: Data collected at echocardiographic examination are based on VARC-2 criteria (Eur J Cardio Thorac Surg 2012; 42: S45–S60). A minimum set of echocardiographic data will be considered: 1) left ventricular (LV) function (EF% based on Simpson's method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade (defined as mild, moderate or severe based on several different echocardiographic indexes as regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local institutional policies). Further assessment of "intra-prosthetic", "peri-prosthetic" or "combined intra+peri-prosthetic" regurgitation will be added.

- b. Active explanation to patients and families about the importance of adherence to follow-up visits for final interpretation of data – with its consequences on Guidelines and current daily practice - will be pursued.

It is expected that linking with regional Social Security Death and Events Master files and using phone contacts with general practitioners will lead to ascertain at least the following follow-up outcome data: 1) All-cause mortality and cardiovascular mortality; 2) MACCE; 3) Reinterventions on the aortic valve; 4) Valve-related adverse events; 5) Repeated revascularization; 6) Clinical efficacy after 30-days; 7) Time-related valve safety.

On the opposite, it is expected a 100% completeness of data related to hospitalization.

19. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Country (2 letters), enrolling Centre (2 letters), and then consecutive number (considered at thousands)(e.g. Mr. XY, third patient enrolled in London = UKLO0003). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, the external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity.

The Central Core Statistical Laboratory analyzing the data will be blinded towards the surgical teams. The Central Core Statistical Laboratory will take responsibility of data managing. Data will be audited from the Central Core Laboratory on a regular basis, as reported previously. All data will be retained in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.

See "Data Management and monitoring" paragraph of the protocol.

- 20.

- a. Continuous variables will be reported as mean and standard deviation or median and interquartile range, as appropriate. Dichotomous and nominal variables will be reported as counts and percentages. Univariate analysis will be performed using the Mann-Whitney U test and Student's t-test for continuous variables (pending the not-normal or normal distribution respectively), the Kruskal-Wallis test (independent multilevel ordinal variables), Wilcoxon test (for paired variables), Fisher exact test and Chi-square test (for dichotomous/nominal variables) and Kaplan-Meier test (for time-dependent dichotomous variables). Multivariable analyses will be performed using logistic regression method (for categorical dependent variable), classification tree analysis (for target variables with a

discrete set of value), linear regression (for continuous dependent variable) and ordinal regression methods (for ordinal dependent variable), as well as Cox-proportional hazards method (to test the effects of covariates on time-dependent dichotomous variables). Significant differences between study groups will be adjusted by using propensity score as covariate or by one-to-one propensity score matching. Matching will be performed using a caliper width of 0.2 of the standard deviation of logit of the propensity score.

- b. Multiple propensity score adjusted analysis will be performed in case of multiple study groups. A Bayesian hierarchical approach will be used in the case of significant variability between centres. Sensitivity analysis will be executed using complete-case analysis. Interim analyses are planned at different time-points (see Ethics and Dissemination), with critical p-values corrected according to the Armitage-McPherson adjustment
 - c. Missing values will be replaced and estimated using multiple imputations.
- 21.
- a. Data Monitoring Committee is not needed because the E-AVR Steering Committee and the Central Core Statistical Lab will take responsibilities of DMC. In particular, data will be collected into a dedicated datasheet with predefined variables. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Country (2 letters), enrolling Centre (2 letters), and then consecutive number (considered at thousands)(e.g. Mr. XY, third patient enrolled in London = UKLO0003). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity. All data will be retained in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. The E-AVR Steering Committee local member has also the responsibility for a continuous auditing of local data, by double-checking and monitoring of data quality and their completeness. Storage, analysis and further auditing of data will be then accomplished by the independent Central Core Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy). External auditing of the dataset will be performed every six months by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator and E-AVR Steering Committee for further data checking and merging. Incomplete or contradictory data with patient identification code will be sent from Central Core Statistical Lab to the E-AVR Steering Committee local member for further data checking, correction and merging. Both the E-AVR Steering Committee (with its members) and Central Statistical Core Lab are free from competing interests (the trial has no sponsor).
 - b. The following interim-analyses have been established:
 - 1. A 3-year outcome study comparing different surgical techniques of TAVR (i.e. trans-apical vs. trans-aortic vs. trans-axillary approach); propensity-matching and risk-adjusted analyses will be executed if baseline differences are identified between the 3 subpopulations; post-hoc statistical analyses will identify outcome-differences between the 3 subgroups
 - 2. An interim-study analyzing 30-day outcome of the first 4000 patients enrolled.
 - 3. A study analyzing 30-day and 1-year outcome of the first 4000 SAVR-patients enrolled. Sub-group analyses will be aimed at compare different surgical accesses (i.e. sternotomy vs. mini-sternotomy vs. mini-thoracotomy); propensity-matching, risk-adjusted and post-hoc analyses will be done appropriately to nullify potential bias in the interpretation of the results, and to compare the results of each surgical subgroup.The results of these interim analyses will be available to all the E-AVR Investigators for data interpretation, with the aim to write “dedicated” scientific papers on these 3 topics. Given that these 3 interim-analyses do not deal with the primary objective of the registry (5-year outcome comparison between SAVR and TAVR), all these results will not have any impact on the possible termination of the trial. Furthermore, investigated treatments (SAVR and

- TAVR) are standards of care according to Current Guidelines and Good clinical practice, therefore no stopping guidelines for the premature termination of the trial can be foreseen at the moment.
22. N.A.: the trial is an observational registry-based cohort study, with collection of data representing standard surgical practice and state-of-the-art perioperative care for cardiac surgical interventions. There are no randomized interventions nor treatments administered per-protocol, therefore no “adverse events” or “unintended effects” directly related to the conductance of the trial can be foreseen.
 23. The Local E-AVR Steering Committee local member is responsible for a continuous active auditing of local data. The Central Core Statistical Lab will perform 6-month external auditing – independent from investigators (no sponsor exists) - by checking the data of a minimum of 40% of the patients.
 24. All Ethical Committee (EC) approvals (from the PI Centre, University of Parma, and from satellite centres) have been obtained.
 25. Important protocol modifications will be discussed inside the E-AVR Steering Committee and -if accepted – communicated to all the E-AVR investigators, as well as to all the ECs of the E-AVR participating Centers by means of “amendment requests”. Only in case of approvals from all ECs the modification will enter the protocol.
 26.
 - a. Written informed consent will be obtained from the patient or patient’s authorized representative prior to enrolment in the Registry. In case of emergent surgery, informed consent will be collected from the patient’s family (or legal representative) before surgery, as well as from the patient after surgery (if unable to give it before intervention). This consent will be waived in case of death or severe neurological damage precluding adequate postoperative patient informed consent. The study will be conducted in accordance with the provisions of the Declaration of Helsinki.
 - b. N.A.: no ancillary studies are planned
 27. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Country (2 letters), enrolling Centre (2 letters), and then consecutive number (considered at thousands)(e.g. Mr. XY, third patient enrolled in London = UKLO0003). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity. Each participating centre will be anonymized by identification with a capital letter. The correspondence between centres and capital letters will only be known by the PI of the study. The Central Core Laboratory analyzing the data will be blinded towards the surgical teams.
 28. No financial and/or competing interests for principal investigators, for the overall trial and each study site
 29. The final dataset is only available to the Central Statistical Core Lab. However, the entire sets of the performed statistical analyses of the primary study and of secondary sub-studies will be available to all E-AVR researchers for the clinical interpretation of data. There is the agreement between E-AVR Investigators and Central Statistical Core Lab that preclude the access of final dataset to all the E-AVR Investigators.
 30. N.A.: given the observational nature of this prospective registry-based cohort study, no ancillary or post-trial care is scheduled, and no harm is expected from the participation to the registry
 31.
 - a. Research findings from the E-AVR registry will be disseminated among the scientific community. They will be presented at international congresses and published in peer reviewed international journals in the fields of cardiac surgery and cardiology. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship. Data collection, analysis and writing process will be monitored by the Steering Committee of the E-AVR, which is made up of the Principal Investigator and a Representing Member from each of the participating

centres. It is expected that periodical E-AVR Steering Committee meetings will occur, every 6 months for the first 2 years, yearly thereafter up to the end of follow-up.

In the event of future merging with other contemporary registries (e.g. collecting data on concurrent interventional – i.e. percutaneous transfemoral, transcarotid or trans-axillary - TAVR procedures), the co-authorship of comparative studies (e.g. between surgical and interventional treatments) will be defined by the Steering Committees of the different registries involved. However, data will not made available for sharing until after publication of the principal results of the study. Thereafter, anonymized individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed used of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements, and value for money. Anonymized data will be shared as long as the patient has agreed and consented to this. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research.

- b. Investigators will be eligible for authorship if they contribute substantially to study planning, data collection, data analysis and interpretation, writing and critical review of the manuscripts. Two authors per centre will be included as main authors of each study. As a member of the Steering Committee, the local Representing Member will take any decisions on co-authorship related to his/her centre on the basis of the above criteria. Those researchers who plan a sub-study, interpret the analysis and write the article will be the first and last authors of the study. When an article is submitted to a journal with a maximum number of co-authors, the Steering Committee will decide on the authors on the basis of their contribution to the design of the study, data collection, interpretation of data, writing, and critical review of the paper.
- c. No plan for granting public access to the full protocol, participant-level dataset and statistical code has been considered

32. **PARTICIPANT INFORMATION LEAFLET**
E-AVR: a Prospective European Multicenter Study on Aortic Valve Replacement

Introduction

You are being invited to take part in a clinical research study. However, before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Taking part in research is voluntary and your medical care will not be affected if you decide not to take part.

If anything is not clear or you would like more information, do not hesitate to ask your research doctor or another member of the research team when you come into hospital (also see contact details at the end of this leaflet).

Talk to others about the study if you wish, such as friends or relatives and take time to decide. If you would like to take part, you will be asked to confirm this before your operation, during your admission or at follow-up after discharge by signing a separate consent form.

What is the purpose of the study?

Severe aortic valve stenosis (abbreviation: SAVS) is a life-threatening disease in which the valve is blocked by the progressive degeneration of its tissue. The same situation is encountered some years after the implantation of a biologic aortic prosthesis, due to the progressive inflammation of prosthetic tissues (biologic prosthetic degeneration). Both conditions are usually treated with the replacement of the patient's failing aortic valve (or prosthesis) with an artificial prosthesis (surgical aortic valve replacement, abbreviation: SAVR, and surgical prosthetic valve replacemet, abbreviation: SPVR). For decades the standard of care has been represented by performing this surgery through a surgical incision of the entire sternum (sternotomy) and with the aid of the so called heart lung machine (i.e., the heart is arrested during the central part of the operation, and vital functions are sustained with this machine). Recently, new surgical techniques have been developed. Indeed, it is possible to proceed to SAVR via different surgical skin incisions (sternotomy, partial sternotomy, small thoracotomy) but always using heart-lung machine; or it is possible to replace the failing valve with new biological prostheses - crimped on a catheter - implanted on the beating heart

through small skin incisions (the latter called transcatheter aortic valve replacement, abbreviation: TAVR).

Native/prosthetic aortic valve replacement is one of the most commonly performed operation in cardiac surgery. Around 100,000 AVR procedures are performed in Europe every year. As with all types of surgery, it carries a risk of complications, usually minor, but there is also a risk of serious complications such as stroke, heart attack or even death. Together with other European centers we want to create a large database (registry) of patients affected by SAVS and undergoing surgical substitution of the failed native/prosthetic aortic valve (named E-AVR Registry) as we think that collection and analysis of data on risk factors, operative techniques, post-operative treatment and secondary prevention strategies will improve treatment and reduce the risk of early and late complications.

Why have I been invited?

You have been invited to take part because you are going to have or you already had an aortic valve replacement. Like you hundreds of patients across Europe will be invited to take part.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide and if you take part you are free to withdraw at any time. If you choose not to take part or to withdraw from the research, you do not have to give any reason for your decision. The operation performed and the care you will receive after will be exactly the same whether you take part in the study or not.

What will happen to me if I take part?

You will be asked to give written consent to take part in the study and you will be given a copy of the consent form and this information leaflet to keep. After discharge we will collect data regarding your pre-operative clinical status, operation and post-operative course. The data collected will be made anonymous prior to be entered into a large European database and shared with other researchers across Europe. Personal identifiable information will not be shared and will remain strictly confidential.

What are the possible disadvantages and risks of taking part?

We do not think that taking part in the study will expose you to any risks or disadvantages. You may be contacted in the future and asked a number of questions regarding your health as a result of cardiac surgery.

What are the possible benefits of taking part?

We think that the information from this research will help us to improve treatment and ameliorate the early and late outcomes for patients having aortic valve replacement (AVR) in the future.

What will happen to the results of the study?

The results of the study will be published in medical journals or shared during medical meetings. Thereafter, anonymous individual patient data will be made available for secondary research, after a proper research approval. You will not be identified in any way. If you would like to receive the results of the study written in plain English, after the research has finished, please contact the study team on the numbers provided at the end of this leaflet.

Further information and contact details:

If you have any concerns or questions about this study please contact the research team on the number or email address provided below. Please use the contact details only for questions about the E-AVR study project. Alternatively you can discuss these with a member of the research team who will come to see you before your operation. Please feel free to ask any further questions before deciding to take part in the study, or at any time during it.

Contact details:

If you want further information contact Dr X X (xxxxxxxxxxxxxxxxxx) or email (xxxxxxxxxxxx).

Other members of the Research Team (email):

Dr. X X (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)

Dr. X X (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)

CONSENT FORM

Name of Researcher: Dr X X

Name of the study: E-AVR: a Prospective European Multicenter Study on Aortic Valve

Replacement

I have had the opportunity to consider the information provided, ask questions and have had these answered satisfactorily	<input type="checkbox"/>
I understand that my participation in the E-AVR registry is voluntary and that I am free to withdraw at any time, without giving any reason	<input type="checkbox"/>
I understand that the information collected will remain anonymous prior to be shared with other European centres that will only have access to non identifiable information	<input type="checkbox"/>
I understand that in the future I may be contacted to be asked questions regarding my clinical status in relation to my AVR operation	<input type="checkbox"/>
I agree to take part in the E-CABG registry	<input type="checkbox"/>

I, the undersigned, have read, understood and agree to the above conditions

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

33. N.A.

BMJ Open

Outcomes comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)

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Manuscripts

Outcomes comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)

F. Onorati¹, R. Gherli², G. Mariscalco³, E. Girdauskas⁴, E.O. Quintana⁵, F. Santini⁶, M. De Feo⁷, S. Sponga⁸, P. Tozzi⁹, M. Bashir¹⁰, A. Perrotti¹¹, A. Pappalardo¹², V.G. Ruggieri¹³, G. Santarpino¹⁴, M. Rinaldi¹⁵, Silva RRG¹⁶, F. Nicolini¹⁷, on behalf of E-AVR Collaborators.

¹Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; ²Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy; ³Department of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK; ⁴Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany; ⁵University Hospital Clinic, Barcellona, Spain; ⁶Cardiac Surgery Unit, University of Genova, Genoa, Italy; ⁷Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy; ⁸Cardiothoracic Department, University Hospital of Udine, Udine, Italy; ⁹Cardiac Surgery Unit, Centre Hospitalier Universitaire Vaudois, Lausanne; ¹⁰Division of Cardiac Surgery, St. Barth Hospital NHS, London, UK; ¹¹Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France; ¹²Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy; ¹³Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN, Hopital Robert Debre', Reims, France; ¹⁴Cardiovascular Center, Klinikum Nürnberg – Paracelsus Medical University, Nuremberg, Germany; ¹⁵Department of Cardiac Surgery, Torino University Hospitals, Turin, Italy; ¹⁶Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy; ¹⁷Div. Cardiac Surgery, University of Parma, Parma, Italy

Corresponding Author: Francesco Onorati, MD PhD – Div. Cardiac Surgery, Dpt. of Surgery, University of Verona Medical School - Piazzale Stefani n.1 – 37126 – Verona, Italy. Phone: 0039 (0)45 8121945; Fax: 0039 (0)45 8123308; Email: francesco.onorati@aovr.veneto.it

ABSTRACT

Introduction: Traditional and transcatheter surgical treatments of severe aortic valve stenosis (SAVS) are increasing in parallel with the improved life-expectancy. Recent randomized trials (RCTs) reported comparable or non-inferior mortality with transcatheter treatments compared to traditional surgery. However, RCTs have the limitation of being a mirror of the predefined inclusion/exclusion criteria, without reflecting the “real clinical world”.

Technological improvements have recently allowed the development of minimally invasive surgical accesses and the use of sutureless valves, but their impact on the clinical scenario is difficult to assess because of the monocentric design of published studies and limited sample-size. A prospective multicentre registry including all patients referred for a surgical treatment of SAVS (traditional, through full-sternotomy; minimally-invasive; or transcatheter; with both “sutured” and “sutureless” valves) will provide a “real-world” picture of available results of current surgical options, and will help to clarify the “grey zones” of current guidelines.

Methods and analysis: E-AVR is a prospective observational open registry designed to collect all data from patients admitted for SAVS, with or without coronary artery disease, in 16 cardiac surgery Centres located in six countries (France, Germany, Italy, Spain, Switzerland, and United Kingdom). Patients will be enrolled over a 2-year period and followed-up for a minimum of 5 years to a maximum of 10 years after enrolment. Outcome definitions are concordant with VARC-2 criteria and established guidelines. Primary outcome is 5-year all-cause mortality. Secondary outcomes aim at establishing “early” 30-day all-cause and cardiovascular mortality, as well as major morbidity, and “late” cardio-vascular mortality, major morbidity, structural and non-structural valve complications, quality of life and echocardiographic results.

Ethics and dissemination: The study protocol is approved by Local Ethics Committees. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship.

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STRENGTHS AND LIMITATIONS OF THIS STUDY:

- The protocol addresses the important question of which surgical treatment offers the most benefits in the management of patients with severe aortic valve stenosis, with or without concomitant coronary artery disease.
- The expected large sample size will guide sub-analyses aimed at identify specific patient characteristics and different risk-profiles, which are better served with alternative surgical techniques.
- The minimum 5-year and maximum 10-year follow-up will provide answers about the mid-to-long term safety and efficacy of recent surgical innovations (i.e. sutureless valves, minimally invasive approaches, surgical TAVR), whose follow-up data are still lacking in current literature
- The present multicentre registry has clearly established aim, inclusion and exclusion criteria, short-term and follow-up primary and secondary endpoints, as well as state-of-the-art methods for data collection and endpoints definition
- Limitations include variations in postoperative and follow-up management, which are based on local Institutional policies, and lack of blinding between the central statistical core-lab performing the analyses and the employed surgical techniques
- The absence of any external sponsor certainly limits research resource allocation, but also guarantees the certainty for the absence of any bias or conflict of interest related to the investigated topics

INTRODUCTION

The prevalence of severe aortic valve stenosis (SAVS) correlates with age, and its treatment is expected to increase parallel to the improved life-expectancy reported in Western Countries (1-2). Traditional surgical aortic valve replacement (SAVR) has been the gold standard of treatment for decades, with well-documented benefits in terms of symptom improvement and survival (3-4). Recent technological advances allowed interventional and surgical transcatheter aortic valve replacements (TAVR), which proved to be effective alternatives to traditional SAVR, in both high-risk and intermediate-risk patients (5-12). Therefore, SAVR and TAVR represent nowadays the standard surgical armamentarium for aortic valve replacement.

Alternative surgical approaches, based on the concept of TAVR (13,14), have in fact been developed. There are on the market two types of “sutureless” valves (i.e. Sorin Perceval and Edwards Intuity) at the moment - aimed at reducing some surgical drawbacks such as cross-clamp time and myocardial ischemia-reperfusion injury (13,15-20) – and it is possible that new “sutureless” valves will enter the market in the next future. Moreover, different mini-thoracotomy and mini-sternotomy approaches to SAVR have been widely adopted by the surgical community - with both “sutured” and “sutureless” valves - in order to reduce surgical trauma, systemic inflammatory response, and major organ morbidity (13,15,16). Various different combinations of minimally invasive accesses and the use of last-generation valves have been reported to date (14,17,18). But despite early enthusiasm about preliminary results with these technological improvements, none of these techniques has yet replaced traditional SAVR in standard surgical practice, mainly because reporting of results of these alternative techniques tends to be biased by single-centre design, limited sample-size, and the strict inclusion/exclusion criteria of the published studies (13,14).

Another “hot topic” in this debate relates to valve durability, given that the long-term durability of both TAVR and sutureless valves is as yet unknown. Indeed, standard “sutured” surgical valves demonstrated excellent durability, both in the very-long term and in very-young adults below the

65-year cut-off age (21-23), which is still the threshold for biological valves recommended by European Society of Cardiology (ESC) / European Association for CardioThoracic Surgery (EACTS) guidelines (24). This issue is of particular interest, given that the use of TAVR has increased in younger intermediate-risk patients, despite recent caveats relating to early degeneration of TAVR (25,26).

Similarly, improved life-expectancy has led to a growing number of patients with degenerated dysfunctioning aortic bioprostheses requiring surgical treatment. Again, surgical aortic prosthetic replacement (SAPR) has been traditionally considered the only treatment strategy for these patients, given the excellent results, recently confirmed by several studies (27,28). Again, transcatheter treatments ("valve-in-valve") have recently demonstrated comparable or sometimes superior results in redo-scenarios (29). Therefore, data on the efficacy, safety and durability of these technological improvements are essential for providing "strong" statements in future guidelines, and for evaluating the extension of these techniques to low-risk and young patients in the future.

Finally, it is well known that critical coronary artery disease (CAD) often coexists with SAVS. Although the standard treatment option for these patients has traditionally been SAVR plus coronary artery bypass grafting (CABG), the introduction of TAVR and minimally invasive surgical alternatives has considerably changed the available options, paving the way to combined less-invasive SAVR+CABG and/or TAVR±PCI (either before, during or after the surgical procedure) (30-34). Again, there is a great deal of confusion on the topic, and there are unanswered questions on the efficacy and safety of these options, as well as on what to expect from late follow-up when compared to the standard practice of SAVR+CABG.

Robust early and follow-up data on the safety and efficacy of surgical TAVR, last-generation sutureless surgical valves, and minimally-invasive approaches compared with standard SAVR, with or without a contemporary (surgical or interventional) treatment of concurrent CAD, are still lacking for a real-world large population of patients at variable surgical risk. Such data is urgently required for the correct allocation of therapy in daily surgical practice. Furthermore, data on quality

of life and functional echocardiographic results with different surgical alternatives might similarly help physicians in decision-making in local “Heart Teams”. Data from a multicentre, real-world, open registry enrolling all patients with SAVS±CAD consecutively referred to several Centres at different European latitudes should help to answer some of these open questions. Here, we describe the rationale and the study protocol of the European Aortic Valve Registry (E-AVR), a multicenter prospective observational open registry on aortic valve surgical practice.

METHODS AND ANALYSIS

Rationale of the study and aim

Improvements in surgical treatment of cardiac diseases can be obtained with the implementation of current techniques and the development of new methods, based on information from large clinical datasets (35). The main strength of a prospective clinical open registry is the high external validity, given that data are collected in the settings of standard clinical practice. Moreover, large sample size enables a better estimation of event rates, and allows the investigation of hard endpoints and outcomes, by means of a wide population of patients from different institutions and with extremely limited exclusion criteria.

Importantly, clinical registries may provide data on long-term outcomes occurring after the study period of a trial (35). They are more practical than randomized controlled trials, require fewer resources, and have less stringent inclusion and exclusion criteria for patient enrolment. Finally, clinical findings from registries have even more significance when patient-populations derive from different geographic areas, with heterogeneous referral pathways, baseline clinical characteristics, and perioperative treatment strategies. All these features substantiate the concept of “a real world practice” underlying any “registry-study”.

Therefore, the rationale of this European multicenter observational open registry is to prospectively collect data on baseline characteristics, treatment options, perioperative management and postoperative outcome of all patients consecutively undergoing surgical treatment of SAVS

(regardless of gradients, AVA or AVAi)±CAD or aortic prosthetic dysfunction±CAD at 16 European university or non-university tertiary hospitals located in six European countries (France, Germany, Italy, Spain, Switzerland, and United Kingdom). The complete list of E-AVR Collaborators is reported in the Appendix.

The primary aim of the study is a 5-year comparison between SAVR and surgical TAVR: we hypothesize to report a 10% inferior 5-year all-cause mortality event rate in SAVR, i.e., we expect that SAVR survival will exceed by 10% (absolute value) that of surgical TAVR. For the purpose of this study, patients will be consecutively enrolled for a 2-year period, and will be followed-up for a minimum of 5 years after the index surgical treatment. Maximum follow-up length will be 10 years after surgery.

The following surgical options will be considered:

- 1) SAVR with mechanical valves
- 2) SAVR with biological valves (either sutured or sutureless, stented or stentless)
- 3) Surgical TAVR (either transapical, trans-axillary, or transaortic)

Similarly, the following surgical approaches will be considered:

- 1) Full sternotomy
- 2) Mini-thoracotomy (either left-sided for TAVR or right-sided for SAVR)
- 3) Partial-sternotomy

Patient allocation to a specific surgical procedure will be based on the local Heart Team decision at each Institution, according to standard clinical practice and current guidelines (2).

A flow-chart of the enrolment criteria and of the surgical techniques considered in the registry is provided in Figure 1.

Criteria for registry-enrolment

The following inclusion and exclusion criteria will be considered:

Inclusion criteria

- Age >18 yy

- Isolated SAVS with or without concomitant aortic valve regurgitation
- Isolated prosthetic aortic dysfunction
- SAVS + coronary artery disease (CAD)
- Prosthetic aortic dysfunction + CAD
- Elective, urgent and emergent procedures
- Endocarditic aetiology

Exclusion criteria

- Patients undergoing concomitant mitral valve surgery, or tricuspid valve surgery, or aortic surgery (i.e. composite aortic valve and ascending aorta replacement with or without circulatory arrest), or atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG)
- Concomitant aortic root procedure (i.e. Bentall operation, David operation, homografts, autografts)
- SAVR with techniques of aortic annular enlargement
- Porcelain aorta
- Pure aortic valve regurgitation
- Percutaneous TAVR (regardless of technique, i.e. either by a completely percutaneous approach or by surgical cut-down)
- Patient refusal

Patients will be recruited in a consecutive series from each institution, and their data collected in a dedicated on-line datasheet. The recruitment period will be 24 months, from 1st November 2017 to 30th October 2019. Every patient will be followed up at 30 days, 6 months, 1 year, and yearly thereafter, up to a minimum of 5 years after the index surgical procedure (Figure 2). Afterwards yearly follow-up will be closed at the completion of the 10th year from surgery for each patient.

On the basis of historical cohort data of local institutions, we expect to enrol a minimum of 4000 patients at the end of the first year, and a minimum of 8000 patients at the end of the second year of enrolment.

Informed consent

Written informed consent will be obtained from the patient or patient's authorized representative prior to enrolment in the Registry. In case of emergent surgery, informed consent will be collected from the patient's family (or legal representative) before surgery, as well as from the patient after surgery (if unable to give it before intervention). This consent will be waived in case of death or severe neurological damage precluding adequate postoperative patient informed consent. The study will be conducted in accordance with the provisions of the Declaration of Helsinki. The study is registered in Clinicaltrials.gov. (No. NCT03143361)

Data management and monitoring

Data will be collected into a dedicated datasheet with predefined variables. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Country (2 letters), enrolling Centre (2 letters), and then consecutive number (considered at thousands)(e.g. Mr. XY, third patient enrolled in London = UKLO0003). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, the external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity.

All data will be retained in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.

Baseline characteristics, operative details and outcome data pertaining hospitalization will be prospectively collected from hospital registries. Variables and events occurring after the index

hospital discharge will be collected from outpatient clinics at the individual Institutions, and linking with regional Social Security Death and Events Master files where available. In case of absent/missing data, variables and events will be collected by direct phone contact with general practitioners, and only if persistently missed by phone contact with patients and families. Events and outcome variables will be adjudicated centrally by a Central Core Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy). In the event of controversy on outcome adjudication, this will be discussed and adjudicated after a final consult between the Central Core Laboratory and the E-AVR Steering Committee. Storage, analysis and auditing of data will be also accomplished by the independent Central Core Laboratory. Auditing of the dataset will be performed every six months by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator and E-AVR Steering Committee for further data checking and merging. Incomplete or contradictory data with patient identification code will be sent from Central Core Statistical Lab to the E-AVR Steering Committee local member for further data checking, review, correction and merging. The entire set of statistical analyses will be available to all E-AVR researchers for the interpretation of data.

Statistical methods

The Central Core Lab (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) will perform all the statistical analyses derived from this registry. It is intended to enrol 8000 patient, of which 60 to 70% will be SAVR and the remainder TAVR (historical data based on Institutional practices). Considering the estimated event rate of 25% in the TAVR patients at 5 years (36), a 2-year accrual time, an anticipated loss-to-follow-up rate of 1.5% (historical data), and the target power of 80% at a 0.05 one-sided log-rank test significance level to detect the hypothesized 10% inferior (absolute improvement) 5-year all-cause mortality rate in favour of SAVR, the calculations showed the overall sample size of the registry to meet the targeted power for all expected scenarios of estimated proportions of SAVR and TAVR patients.

Similar calculation shows that, considering the estimated 30-days all-cause mortality event rate of 5.0% after SAVR and of 5.5% after TAVR (0.5% absolute difference) in intermediate-risk patients (37), the overall sample size of the registry also meets the targeted 80% power to detect a difference as small as 0.5% in 30-days all-cause mortality event rate in favour of SAVR. Other secondary endpoints will serve as exploratory analyses, possibly useful for sample size estimation of future clinical trials.

Statistical calculations were accomplished with PASS 14.0 Power Analysis and Sample Size Software (2015) statistical package (NCSS, LLC; Kaysville, Utah, USA - ncss.com/software/pass). Continuous variables will be reported as mean and standard deviation or median and interquartile range, as appropriate. Dichotomous and nominal variables will be reported as counts and percentages. Univariate analysis will be performed using the Mann-Whitney U test and Student's t-test for continuous variables (pending the not-normal or normal distribution respectively), the Kruskal-Wallis test (independent multilevel ordinal variables), Wilcoxon test (for paired variables), Fisher exact test and Chi-square test (for dichotomous/nominal variables) and Kaplan-Meier test (for time-dependent dichotomous variables). Log-rank test will be used to compare the 5-year all-cause mortality rate between SAVR and surgical TAVR. Multivariable analyses will be performed using logistic regression method (for categorical dependent variable), classification tree analysis (for target variables with a discrete set of value), linear regression (for continuous dependent variable) and ordinal regression methods (for ordinal dependent variable). Cox-proportional hazards method will test the effects of covariates on time-dependent dichotomous variables; the model's proportional hazard assumption will be checked using the Schoenfeld residuals test. Significant differences between study groups will be adjusted by using propensity score as covariate or by one-to-one propensity score matching. Matching will be performed using a caliper width of 0.2 of the standard deviation of logit of the propensity score. Multiple propensity score adjusted analysis will be performed in case of multiple study groups. A Bayesian hierarchical approach will be used in the case of significant variability between centres.

Missing values will be replaced and estimated using multiple imputations. Furthermore, sensitivity analysis will be executed using complete-case analysis. Interim analyses are planned at different time-points (see Ethics and Dissemination). Critical p-values of accomplished interim analyses will be corrected according to the Armitage-McPherson adjustment (38).

Early and late endpoints

Outcome endpoints will be defined according to current guidelines, i.e. VARC-2 definitions (39) and Guidelines for reporting mortality and morbidity after cardiac valve interventions (40).

In more detail, the following outcome variables will be collected:

Primary outcome of the E-AVR registry: 5-year all-cause mortality

Secondary outcomes of the E-AVR registry: these will be dichotomized into “early” at 30-day (i.e. during hospitalization, at home if discharged, or during “rehab-hospitalization” at any time point if never discharged home) and “late” (after the patient is discharged home):

- 1) Early secondary outcomes: all-cause mortality, cardiovascular mortality, stroke, acute myocardial infarction (AMI) (41) , postoperative need for prolonged use of inotropes (>72 hours), postoperative need for intra-aortic balloon pump (IABP) or extracorporeal mechanical oxygenation (ECMO), surgical site infection, blood losses and use of blood products (during hospitalization for the index surgical procedure), nadir hematocrit, nadir hemoglobin, re-sternotomy for bleeding, atrial fibrillation (first event and number of events), cardiac conduction disturbances, need for new permanent pace-maker implantation, acute kidney injury (following AKIN classification), pericardial effusion requiring treatment, length of stay in the intensive care unit, length of in-hospital stay (for the index procedure), device success, early safety, clinical efficacy, time-related valve safety, echocardiographic data of prosthesis performance, early repeat surgery for failure of the index procedure (any “redo” before discharge home or to rehabilitation clinic).
- 2) Late secondary outcomes (collected starting from discharge to the end of the 10th year after the index procedure): cardiovascular mortality, all-cause mortality (from 1 to 4 years after

surgery, then from 6 to 10 years), stroke, acute myocardial infarction, reintervention on the aortic prosthesis, repeat revascularization (either with percutaneous coronary intervention or CABG), prosthetic thrombosis, embolism, bleeding events, structural valve deterioration, paravalvular leakage, prosthetic endocarditis, need for permanent pacemaker, need for implantable cardioverter-defibrillator, MACCE (defined as a composite end-point including any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, repeated revascularization), time-related valve safety, quality of life (QoL; defined according to Short Form-8 questionnaire; QoL will be assessed during follow-up visits at outpatient clinics or, if other methods are not possible, by telephone interview); echocardiographic data of prosthesis performance.

Echocardiographic data of prosthesis performance are defined according to the Valve Academic Research Consortium-2 definitions (38). All echocardiographic data will be collected from 3rd level nationally and/or internationally certified Institutional Echo Laboratories: 5% of these echocardiographic exams will be reviewed centrally (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) by third level certified echocardiographers. Collection of data is under the responsibility of the Steering Committee local member at each participating Centre. Data will be audited from the Central Core Laboratory on a regular basis, as reported previously.

Outcomes and their definition criteria are described in detail in the following section of this article.

Data collection

Participating Centre: Each participating Centre will be anonymized by identification with a capital letter. The correspondence between Centres and capital letters will only be known by the PI of the study. The Central Core Laboratory analyzing the data will be blinded towards the surgical teams.

Units of measurement: Laboratory data will be collected according to fixed units of measurement in order to avoid any problem stemming from differences in units used by the various participating

centres, during data merging and analysis. The fixed units of measurement are reported in the dedicated CRF datasheet.

Laboratory parameters: baseline levels of haemoglobin, haematocrit, platelets, blood glucose, HbA1c, C-reactive protein, TT-INR and albumin will be collected.

Hypertension: arterial blood pressure > 140/90 mmHg or anti-hypertensive treatment.

Diabetes: diabetes mellitus requiring diet, oral or insulin treatment.

Preoperative creatinine levels: this parameter is obtained on the day before surgery and is expressed in $\mu\text{mol/L}$.

Chronic Kidney Disease: the severity of renal failure will be classified as shown in Table 1. It is stratified by the estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease Study Group modified formula (42). eGFR for calculation of the EuroSCORE II (43) will be estimated using the Cockcroft-Gault formula (44) according to the criteria of this risk scoring method.

Dialysis: peritoneal or hemo-dialysis before surgery.

Chronic obstructive pulmonary disease (COPD): any long-term use of bronchodilators or steroids for lung disease.

Oxygen therapy: long-term oxygen therapy for respiratory failure.

Liver disease: different degrees of liver failure stratified according to the Child-Pugh classification (45).

Active neoplasia: any active malignancy.

Preoperative stroke: any preoperative focal or global neurological syndrome caused by ischemia or haemorrhage not resolving within 24 hours.

Neurological dysfunction: disabling outcomes in ambulation and / or normal motor functions, according to EuroSCORE II definition (43).

Extracardiac arteriopathy: one or more of the following: claudication, carotid occlusion or >50% stenosis, amputation for arterial disease, previous or planned intervention on the abdominal aorta, limb arteries or carotids.

Preoperative ECG: sinus rhythm, or atrial fibrillation; or first degree AV block; or right bundle block; or left bundle block; or pacemaker rhythm.

Preoperative myocardial infarction: any preoperative myocardial infarction.

Previous vascular surgery: history of surgical or endovascular procedure of the thoracic or abdominal aorta and/or the iliac-femoral arteries.

Previous cardiac surgery: one or more previous cardiac operations requiring opening of the pericardium.

Type of previous cardiac surgery: description of previous cardiac operation.

Previous aortic valve replacement: description of prosthesis and date of operation.

Previous percutaneous coronary intervention: any previous percutaneous coronary intervention.

Etiology of aortic valve disease: native valve disease (degenerative; rheumatic; endocarditic) or prosthetic valve disease.

Endocarditis: any diagnosis of valve endocarditis made by the Heart Team and/or antibiotic treatment for endocarditis at the time of surgery. Subclassification into acute, subacute, and healed endocarditis based on Current Guidelines will be added (46).

Endocarditis etiology: microbe isolated for the diagnosis of endocarditis

NYHA functional classes: defined according to the criteria listed in Table 2 (47).

Aortic valve stenosis: severity of aortic valve stenosis before surgery will be graded as moderate or severe according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (48).

Aortic valve regurgitation: Severity of aortic valve regurgitation before surgery will be graded in classes from 0 to 3, and the grade of severity will be evaluated according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (48).

Associated critical coronary artery disease: presence of stenosis of at least 70% in any major epicardial coronary artery. Number of main vessels involved will be recorded. Patients with stenosis of the left main coronary artery will be considered as having at least two-vessel disease.

Associated left main coronary artery disease: Any LMSD > 50%

Mitral valve regurgitation: severity of concurrent mitral valve regurgitation - though not requiring surgery - will be graded in classes according to 2014 AHA/ACC guidelines for the management of patients with valvular heart disease (48).

Left ventricular function: last measured left ventricular ejection fraction before surgery (in any case before induction of anesthesia).

Pulmonary hypertension: absent: <31 mmHg; moderate: 31-55 mmHg; severe: >55 mmHg, according to EuroSCORE II definition (43). Systolic pulmonary pressure will be estimated at echocardiography, at least before induction of anesthesia.

Preoperative echocardiography data: aortic valve area, peak transvalvular gradient, mean transvalvular gradient, aortic annulus diameter, maximum jet velocity (TTE) will be recorded.

Preoperative multislice CT scan data: annulus circumference; valvular area; calcium score (collected for all surgical TAVR, and only if available for other surgical techniques)

Diseased ascending aorta: any sign of diffuse atherosclerosis in the ascending aorta at palpation or epiaortic ultrasound (porcelain aorta is not considered).

Montgomery classification: if available, echocardiographic Montgomery classification of aortic atheromas will be provided.

Preoperative antithrombotic or antibiotic drug treatment: data on all antithrombotic drugs administered before surgery will be collected. The date of pause of drug treatment is the last day the patient received the drug. Data on any oral or intravenous antibiotics administered preoperatively without prophylaxis purpose, i.e. for any preoperative infectious condition, will be collected.

Elective surgery: elective procedure scheduled for stable aortic valve disease.

Urgent surgery: procedure indicated by medical factors which require the patient to stay in hospital to have operation before discharge.

Emergency surgery: procedure performed before the beginning of the working day after the decision to operate.

Frailty: Preoperative patient's frailty is graded according to Geriatric Status Scale, as proposed by Rockwood et al (49).

Critical preoperative status: ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anesthetic room, preoperative inotropes or IABP, preoperative acute renal failure (anuria or oliguria <10ml/hr), according to EuroSCORE II definition (43).

EuroSCORE II: this risk score is calculated using the on-line calculator available at <http://www.euroscore.org/calc.html> and reported as a percentage. The risk factors included in the EuroSCORE II and collected in the E-AVR registry are defined according to the EuroSCORE II criteria (42).

STS score: this risk score is calculated using the on-line calculator available at <http://riskcalc.sts.org/stswebriskcalc/#/> and reported as a percentage. The risk factors included in the STS score and collected in the E-AVR registry are defined according to the STS score criteria (50).

Surgical chest access: classified as 1) full sternotomy; 2) minithoracotomy; 3) partial-sternotomy.

Aortic valve replacement data: classified as 1) mechanical prosthesis; 2) stented biological prosthesis; 3) stentless biological prosthesis; 4) sutureless biological prosthesis; 5) trans-apical TAVR; 6) transaortic TAVR. The description of model and diameter of the prosthesis implanted and possible need for proctored procedure will also be collected.

Other intraoperative data: type of cardioplegia and its temperature, duration of extracorporeal circulation (ECC), nadir temperature of ECC, and aortic cross-clamping time, need for re-aortic cross-clamping for any reason (paravalvular leak, coronary obstruction, annular rupture/hematoma, re-construction of CABG, etc), as well as details of TAVR implantation including sheath size, pre-implantation valvuloplasty, occurrence of valve-in-valve emergency procedure, the number of valves implanted, prosthesis migration, recapturing and re-positioning of the valve, post-procedural dilation, amount of contrast medium administered will be collected.

CABG details: Details of types of conduit and target vessel will be reported (e.g.: LIMA-LAD, RIMA-Dx, RA-MO. SV-DIAG): The following specifications for conduits will be used: LIMA: left internal mammary artery; RIMA: right internal mammary artery; RA: radial artery; GEA: gastro-epiploic artery; SV: saphenous vein. The following target acronyms will be used: DA: anterior descending; DIAG: diagonal; RX: right coronary (trunk); PDA: posterior descending; PL: postero-lateral; OM: obtuse marginal. In the event of sequential grafting, the prefix "seq" will be used before targets (e.g. LIMA-seq DIAG-DA)

Other CABG details: number of distal anastomoses, completeness of revascularization.

30-day all-cause mortality: defined as the sum of cardiovascular and non-cardiovascular, the latter defined as any death in which the primary cause is clearly related to another condition not contemplated by the definition "cardiovascular" (e.g. trauma, cancer, etc.), as in VARC-2 definition (39), but occurring within 30-days or during index procedure hospitalization if the postoperative length of stay is longer than 30 days.

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3 *30-day cardiovascular mortality*: based on VARC-2 definition (39) and occurring within 30-days or
4 during hospitalization for the index procedure if the postoperative length of stay is longer than 30
5 days. This includes: 1) death due to proximate cardiac cause (e.g. myocardial infarction, cardiac
6 tamponade, worsening heart failure, low cardiac output syndrome, etc.); 2) death caused by non-
7 coronary vascular conditions (e.g. pulmonary embolisms, stroke, aortic rupture or vascular
8 dissection, etc); 3) all procedure-related deaths (including those related to a complication of the
9 procedure or a treatment for a complication of the procedure); 4) all valve-related deaths including
10 valve dysfunction (structural or non-structural) and other valve-related adverse events; 5) sudden or
11 unwitnessed death
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14 *Type 5 myocardial infarction*: defined according to the recent criteria defined by Moussa et al. (51)
15 (Table 3).
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18 *Atrial fibrillation*: any new paroxysmal/permanent atrial fibrillation episode requiring or not
19 requiring pharmacological or electrical cardioversion attempts. Number of recurrences will be also
20 collected.
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23 *Cardiac conduction disturbances*: defined as a new left bundle branch block, right bundle branch
24 block, or AV-block (1st, 2nd or 3rd degree). Diagnosis will be based on official medical reports from a
25 consultant cardiologist. In case of progressive bradi-arrhythmias, the evolution of the arrhythmias
26 will be collected.
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29 *Need for permanent PMK*: collected as a dichotomic variable. Type of permanent pacing set-up
30 (e.g. AAI, VVI, DDD, etc) will be collected.
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33 *Postoperative neurologic damage*: classified as: 0) absent; 1) disabling stroke; 2) non-disabling
34 stroke; 3) TIA, based on definitions of VARC-2 consensus (39).
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37 *Stroke classification*: 1) ischemic; 2) haemorrhagic; 3) unknown, according to VARC-2 consensus
38 (39). The diagnosis and nature of stroke will be supported by CT or MRI imaging and confirmed by
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Prolonged use of inotropes (>72 hours): This refers to the use of inotropes for >72 hours after the index operation. The type, dose and duration of administered inotropes will be also collected.

Cardiogenic shock: postoperative critical hemodynamic condition requiring mechanical ventricular-assist devices or high-dose inotropes with evidence of peripheral malperfusion. Coexistence of a cardiac index < 1.8 l/min/m² despite adequate correction of all the coexisting preload, afterload, electrolyte and gas-analyses abnormalities will be pursued with the aid of different hemodynamic monitoring methods, according to local Institutional policies (e.g. echocardiography, Swan-Ganz catheter, PICCO, PRAM, Vigileo, etc.).

LABP: intra- or postoperative insertion of an intra-aortic balloon pump device.

ECMO: intra- or postoperative insertion of an extracorporeal mechanical pump/oxygenation device.

Bleeding: classified as 1) life-threatening or disabling bleeding; 2) major bleeding; 3) minor bleeding, according to the recent definition criteria reported by the VARC-2 document (39).

Blood loss 12 hours after surgery: the amount of postoperative blood losses from mediastinal drainages 12 hours after surgery. Intraoperative blood losses are not taken into account. Nadir haemoglobin and nadir haematocrit will be collected.

No. of transfused RBC units at hospital discharge: total amount of RBC units intra- and/or postoperatively transfused, from the beginning of surgery to the day of discharge.

No. of transfused fresh frozen plasma, pooled human plasma (Octaplas), and/or platelets units at hospital discharge: This refers to the transfusion of these blood products from the beginning of surgery to the day of discharge.

Reintervention for bleeding: any reoperation for postoperative bleeding, regardless of concomitant hemodynamic problems.

Reintervention for hemodynamic problems: any reoperation for hemodynamic instability. This can also be associated with excessive bleeding: in this case, both categories (“Reintervention for bleeding” and “Reintervention for hemodynamic problems”) will be marked.

Pericardial effusion requiring treatment: any pericardial effusion requiring interventional treatment (e.g. pericardiocentesis, subxifoid drainage, resternotomy, etc) due to cardiac tamponade, sub-tamponade, or hemodynamic instability refractory to conservative treatment-strategies.

Acute renal failure: severity of acute renal failure after surgery will be graded in AKIN stages from 1 to 3, according to VARC-2 criteria (39).

Highest postoperative creatinine level: the highest level of serum creatinine detected after surgery during the in-hospital stay. Creatinine levels will be reported in $\mu\text{mol/L}$

Renal replacement therapy: the need for renal replacement therapy will be dichotomized into “temporary” or “permanent” (the latter in the event of death while on renal replacement therapy, or if discharged on renal replacement therapy, or in case of life-long need). Type of renal replacement therapy (e.g. dialysis, CVVH, SCUF, etc.) will be also collected as a note.

Gastrointestinal complications: any gastrointestinal complication requiring endoscopy and/or surgical treatment. Endoscopic diagnostic procedures without any associated interventional procedure (diagnostic only) will not fit this definition.

Post-operative infection: classified as: 1) surgical site infection; 2) organ infection (respiratory, urinary, gastrointestinal infection); 3) systemic infection (sepsis) 4) index valve/device infection.

Wound complications are graded according to the Centre for Disease Control and Prevention definitions of surgical site infections (52). Any surgical site infection occurring within three months after surgery will be considered as a postoperative wound infection.

Early repeated intervention for index intervention failure: This refers to any surgical or percutaneous procedure on the aortic valve and/or the coronary arteries, performed during the same hospital stay for any prosthesis-related or graft-related complication. These events will be marked as occurring or not, and further detailed in their nature (“valvular early procedure”, “coronary early procedure” or “coronary + valvular early procedure”). Further details will be collected as explanatory notes.

Length of stay in the intensive care unit: number of hours spent in the intensive care unit from surgery. Readmissions to intensive care unit will be considered and included in the number. estimation.

Length of in-hospital stay: number of days spent into hospital (ICU-stay will be added) from the day of surgery to hospital discharge to any other hospital ward, rehabilitation unit or home.

Drug antithrombotic treatment at discharge: collected dichotomic (yes/no) for each of the following drugs: 1) vitamin-K antagonists; 2) new oral anticoagulants; 3) antiplatelets. Further details on type and dose of each drug will be added as a note.

Type of discharge: discharge will be categorized according to the Italian NIH classification, as follows: 1) death; 2) discharged home; 3) discharged to rehabilitation clinic; 4) voluntary discharge; 5) transferred to other hospital for acute complications; 6) transferred to other hospital for other reasons; 7) transferred to rehab/other hospital for chronic complications; 8) ordinary discharge + nurse assistance at home; 9) dismissal.

NYHA at follow-up: NYHA class will be assessed at hospital discharge, at 6 months, 1 year, yearly up to the 5th-year follow-up, and then yearly up to follow-up closure (10 years).

Date of events: during follow-up, the date of each possible event will be collected as “dd/mm/yyyy”

Follow-up death: death occurring after hospital-discharge. Further dichotomization into cardiovascular and all-cause mortality is based on VARC-2 criteria (39).

Follow-up stroke: any focal or global neurological syndrome occurring after discharge and caused by ischemia and/or haemorrhage not resolving within 24 hours. The diagnosis and nature of stroke will be made on the basis of findings from brain CT, or MRI, or based on the medical report of a consultant neurologist.

Follow-up myocardial infarction: any myocardial infarction occurring after discharge and requiring medical, interventional or surgical treatment occurring after discharge.

Follow-up re-intervention on the aortic valve: re-intervention is defined as any surgical or percutaneous interventional treatment that replaces (or repairs) an aortic prosthesis implanted at the time of the index procedure which is dysfunctional for either structural or non-structural reasons.

Follow-up aortic valve-related adverse event: this includes: 1) embolism; 2) valve thrombosis; 3) bleeding events; 3) structural valve deterioration; 4) paravalvular leakage; 5) operated valve endocarditis; 6) haemolysis, based on the definitions of current Guidelines for reporting mortality and morbidity after cardiac valve interventions (40).

Follow-up repeated revascularization: any CABG and/or PCI performed after discharge for coronary graft dysfunction and/or valve-related coronary complication. Any revascularization due to the progression of an untreated subcritical (at the time of the index procedure) coronary target will not be considered.

Need for implantable cardioverter-defibrillator: collected as a dichotomous variable (yes/no)

Composite outcome: according to VARC-2 definitions (39), this includes: 1) device success (absence of procedural mortality with correct positioning of a single prosthesis and with intended performance of the prosthesis); 2) early safety at 30 days (composite endpoint of all-cause mortality, all strokes, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary obstruction requiring intervention, major vascular complication or valve-related dysfunction requiring repeat procedure); 3) clinical efficacy after 30 days (composite endpoint of all-cause mortality, all strokes, hospitalization for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV, valve related dysfunction); 4) time-related valve safety (composite endpoint of structural valve deterioration requiring repeat procedure, prosthetic valve endocarditis, thrombosis, thrombo-embolic events or valve-related VARC bleeding).

Follow-up MACCE: defined as a composite end-point occurring after the 30-day time-point (considered as hospitalization, 30th day if discharged home, or during “rehab-hospitalization” at any time point if never discharged home), and including any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, follow-up repeated revascularization

Assessment of post procedural aortic prostheses performance: data on valve and prosthetic performances will be recorded according to medical reports from a consultant echocardiographer. Data will be collected before surgery, before hospital discharge, at 30 days after surgery, 6 months, 1 year after implantation, yearly thereafter up to the follow-up closure (10th year). Data collected at echocardiographic examination are based on VARC-2 criteria (39), and aimed at exploring prosthetic valve-performance and ventricular performance. A minimum set of echocardiographic data will be considered, as follows: 1) left ventricular (LV) function (EF% based on Simpson’s method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade (defined as mild, moderate or severe based on several different echocardiographic indexes as regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local institutional policies). Further assessment of “intra-prosthetic”, “peri-prosthetic” or “combined intra+peri-prosthetic” regurgitation will be added.

Short-Form 8 SF-8 Health Survey questionnaire: will be based on eight questionnaire items reported in Table 4 (53). This examination will be administered before surgery, at hospital discharge, at 30-days, at 6 months, at 1 year, yearly thereafter up to the 5th-year of follow-up, then at follow-up closure (10th year).

ETHICS AND DISSEMINATION

The study is approved by the local Institutional Review Boards/Ethical Committees, according to local or national guidelines for approval of registry studies. Patient’s informed consent will be always obtained.

This multicenter, prospective open registry is designed with the aim of investigating a number of controversial issues regarding current treatment-options and risk factors for the surgical therapy of SAVS with or without CAD. Several studies and information are expected to derive from the data collected in the registry. These data will provide further knowledge on the mechanisms leading to adverse events during or after surgery for SAVS and help their prevention, thus allowing a “tailored” surgical approach for the treatment of this disease.

Several studies are planned at the moment:

Primary study:

- 1) A 5-year study comparing all-cause mortality between SAVR and surgical TAVR. We expect to report a 10% superiority of SAVR vs. TAVR according to sample size calculation and literature data (7,36). Either adjusted and unadjusted analyses will be performed, although the adjusted analysis will be of clearer value, given the expected different risk-profiles of SAVR and TAVR patients. Adjustment will be made by entering as covariates all demographic and anthropometric data, risk scores, comorbidities, and those baseline characteristics (key echocardiographic and surgical/technical factors included) having a different distribution at univariate analyses between the 2 patient-populations. This study will also report echocardiographic data, functional status, quality of life, incidence of cardiovascular mortality, reinterventions on the aortic valve, and incidence of structural valve deterioration between “all-comers” surgical TAVR and SAVR. The study is expected 6 years after the start of data collection and it is aimed at being presented in a major European cardiology journal

Secondary sub-studies

- 2) An observational study providing results of the different surgical techniques to treat SAVS - in terms of “all-cause” and “cardiovascular” mortality, major morbidity and VARC-2 follow-up outcome analysis - at the end of the 5th-year follow-up of the last patient enrolled. We aim at present this study in a major cardio-thoracic surgical Congress and publish it in a

- Congress-satellite Journal. This study is expected after 6 years from the start of data collection.
- 3) A study comparing early and 5-year follow-up outcome of mechanical vs. biological prostheses in young population (<70 years of age). Propensity-matching and risk-adjusted analyses will be performed. It is aimed at being presented in a major American journal of the cardiology field. This study is expected after 6 years from the start of data collection.
- 4) A study comparing early and 5-year follow-up outcome of stented vs. stentless vs. sutureless bioprostheses vs. surgical TAVR in small annuli (≤ 21 mm). Propensity-matching and risk-adjusted analyses will be performed. Post-hoc analysis will help elucidate between-group differences. It is aimed at being presented in a major European cardiology journal of the cardiology field. This study is expected after 6 years from the start of data collection.
- 5) A study comparing early and 5-year follow-up outcome of sutured (both stented and stentless) bioprostheses vs. sutureless bioprostheses. Propensity-matching and risk-adjusted analyses will be performed. It is aimed at being presented in a major American or European journal of the cardiology field. This study is expected after 6 years from the start of data collection.
- 6) A 5-year outcome study comparing SAVR vs. surgical TAVR in intermediate-risk patients. Propensity-matching and risk-adjusted analyses will be performed. This study is aimed at being presented in a major European journal of the cardiology field. It is expected after 6 years from the start of data collection.
- 7) A 3-year outcome study comparing different surgical techniques of TAVR (i.e. trans-apical vs. trans-aortic vs. trans-axillary approach). Propensity-matching and risk-adjusted analyses will be executed if baseline differences are identified between the 3 subpopulations. Post-hoc statistical analyses will identify outcome-differences between the 3 subgroups. This study is aimed at being presented in a European journal of the field. This study is expected after 4 years from the start of data collection.

- 8) A 5-year outcome study resembling the previous one for final outcome data. This study is aimed at being presented in a major American journal of the field . It is expected after 6 years from the start of data collection.
- 9) An interim-study analyzing 30-day outcome of the first 4000 patients enrolled. This study is expected after 1 year from the start of data collection. It is aimed at being presented in a major European cardio-thoracic Meeting and satellite journal.
- 10) A study analyzing 30-day outcome and 1-year follow-up outcome of the first 4000 SAVR-patients enrolled. Sub-group analyses will be aimed at compare different surgical accesses (i.e. sternotomy vs. mini-sternotomy vs. mini-thoracotomy). Propensity-matching, risk-adjusted and post-hoc analyses will be done appropriately to nullify potential bias in the interpretation of the results, and to compare the results of each surgical subgroup. This study is expected after 2 years from the start of data collection. It is aimed at being presented in a major European cardio-thoracic Congress and satellite journal
- 11) A study analyzing the 5-year outcome after SAVR+CABG vs. TAVR±PCI (regardless of the surgical access for SAVR and TAVR) in patients admitted with contemporary critical aortic stenosis and coronary disease. Propensity-score and risk-adjusted analyses will be done as appropriate for a correct interpretation of data. Particular attention will be focused on the role of “incomplete revascularization” and of different techniques of “staged TAVR and PCI” in the transcatheter group. This study is expected after 6 years from the start of data collection. It is aimed at being presented in a major European cardio-thoracic Congress and satellite journal
- 12) A 10-year study comparing all-cause and cardiovascular mortality, echocardiographic data, functional status, quality of life, incidence of reinterventions on the aortic valve, and incidence of structural valve deterioration between SAVR and surgical TAVR. This study is expected after 11 years from the start of data collection and it is aimed at being presented in a major European cardiology journal

13) A 10-year study comparing all-cause and cardiovascular mortality, echocardiographic data, functional status, quality of life, incidence of reinterventions on the aortic valve and incidence of structural valve deterioration between SAVR with “sutured” valves and SAVR with “sutureless” valves. This study is expected after 11 years from the start of data collection and it is aimed at being presented in a major cardiology journal

For all the above-mentioned studies considering propensity-score method, demographic data, gender, EuroSCORE-2, STS Score, NYHA functional class, frailty scale, left ventricular function, comorbidities, and all those baseline characteristics (anthropometric data, key laboratory tests, echocardiographic parameters and surgical factors included) having a different distribution at univariate analyses between the 2 patient-populations and/or potentially acting as bias will be included in the derivation of the propensity score. Furthermore, the variable “participating centre” will always enter the propensity-score model, in order to account for “undetectable” differences between participating centres (e.g. perioperative care protocols, institutional protocols, ethnicity, environmental factors, etc. not collected in the Registry). Subsequent analyses with matched cohorts will be performed accounting for the matched nature of the data.

Further studies aimed at peculiar sub-group analyses are not considered at this moment, but the E-AVR Steering Committee will evaluate any study/sub-study proposal from any researcher involved in the Registry, and accept/reject it by vote after review and discussion about its feasibility.

Therefore, research findings from the E-AVR registry will be disseminated among the scientific community. They will be presented at international congresses and published in peer reviewed international journals in the fields of cardiac surgery and cardiology. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship. Data collection, analysis and writing process will be monitored by the Steering Committee of the E-AVR, which is made up of the Principal Investigator and a local Representing Member from each of the participating centres. It is expected that periodical E-AVR

Steering Committee meetings will occur, every 6 months for the first 2 years, yearly thereafter up to the end of follow-up. A complete list of the E-AVR Collaborators is reported in Appendix. The Members of the Steering Committee will take responsibility for the quality of data through local audit.

Investigators will be eligible for authorship if they contribute substantially to study planning, data collection, data analysis and interpretation, writing and critical review of the manuscripts. Two authors per centre will be included as main authors of each study. As a member of the Steering Committee, the local Representing Member will take any decisions on co-authorship related to his/her centre on the basis of the above criteria. Those researchers who plan a sub-study, interpret the analysis and write the article will be the first and last authors of the study. Analyses will be performed and/or monitored by an independent Central Core Statistic Laboratory. When an article is submitted to a journal with a maximum number of co-authors, the Steering Committee will decide on the authors on the basis of their contribution to the design of the study, data collection, interpretation of data, writing, and critical review of the paper.

In the event of future merging with other contemporary registries (e.g. collecting data on concurrent interventional – i.e. percutaneous transfemoral, transcarotid or trans-axillary - TAVR procedures), the co-authorship of comparative studies (e.g. between surgical and interventional treatments) will be defined by the Steering Committees of the different registries involved. However, data will not be made available for sharing until after publication of the principal results of the study. Thereafter, anonymized individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements, and value for money. Anonymized data will be shared as long as the patient has agreed and consented to this. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research.

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COMPETING INTEREST STATEMENT

None to declare.

FIGURE LEGENDS

Figure 1. Flowchart of enrolment criteria and surgical techniques considered in the registry (CAD: coronary artery disease)

Figure 2. Flowchart of time-points for data collection

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AUTHOR’S CONTRIBUTIONS:

F. Onorati: Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

R. Gherli: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

G. Mariscalco: Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

E. Girdauskas: Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

E.O. Quintana: Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

F. Santini: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

M. De Feo: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

S. Sponga: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

P. Tozzi: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

M. Bashir: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

A. Perrotti: Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

A. Pappalardo: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

V.G. Ruggieri: Conception of the study, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

G. Santarpino: drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspects of the study

M. Rinaldi: Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study

Silva RRG: Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing

F. Nicolini: Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing

TABLE 1: Stages of renal failure.

Stages	eGFR level (mL/min/1.73 m2)
1	90 or above
2	89 to 60
3a	59 to 44
3b	44 to 30
4	29 to 15
5	Less than 15 or on dialysis

TABLE 2: New York Heart Association functional classes.

<i>Class</i>	<i>Definition</i>
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest
IV	Severe limitations. Experiences symptoms even while <i>at rest</i> . Mostly bedbound patients

TABLE 3: Definition criteria of type V myocardial infarction.

Baseline condition	Definition
1. In patients with normal baseline CK-MB or cTn (I or T)	The peak CK-MB measured within 48 hours of the procedure rises to $\geq 10 \times$ the local laboratory upper limit of normal (ULN), or to $\geq 5 \times$ ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the procedure rises to $\geq 70 \times$ the local laboratory ULN, or $\geq 35 \times$ ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB.
2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Table 4: SF-8TM Health Survey

Date _____ Name _____

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. For each of the following questions, please mark an [x] in the one box that best describes your answer.

I. Overall, how would you rate your health during the past 4 weeks?

Excellent Very Good Good Fair Poor Very Poor

II. During the past 4 weeks, how much did physical health problems limit your physical activities (such as walking or climbing stairs)?

Not at all Very little Somewhat Quite a lot Could not do physical activities

III. During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?

Not at all Very little Somewhat Quite a lot Could not do daily work

IV. How much bodily pain have you had during the past 4 weeks?

None Very mild Mild Moderate Severe Very severe

V. During the past 4 weeks, how much energy did you have?

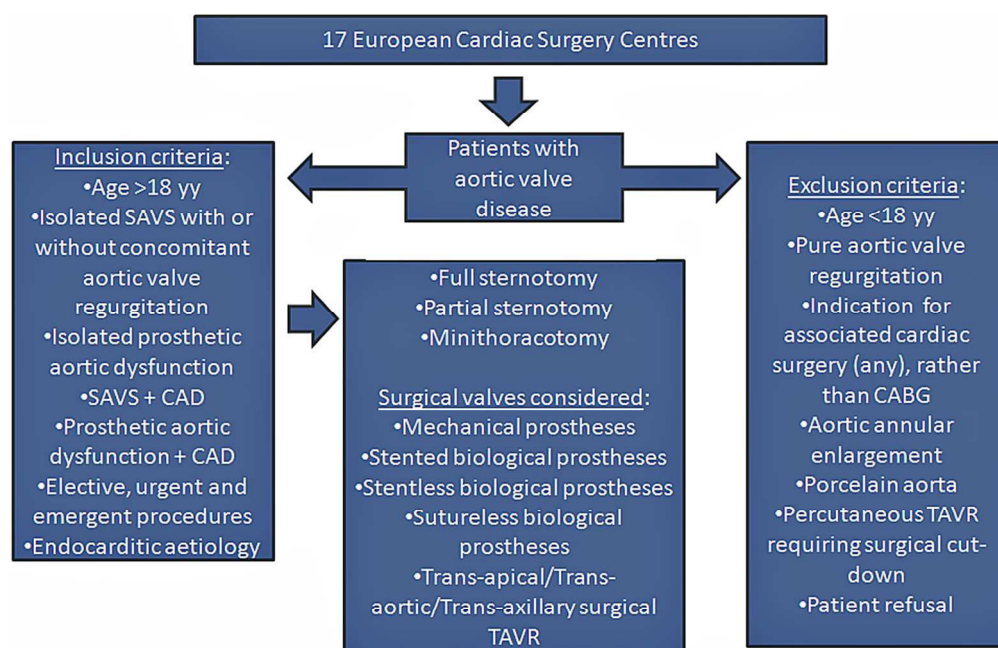
Very much Quite a lot Some A little None

VI. During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?

Not at all Very little Somewhat Quite a lot Could not do social activities

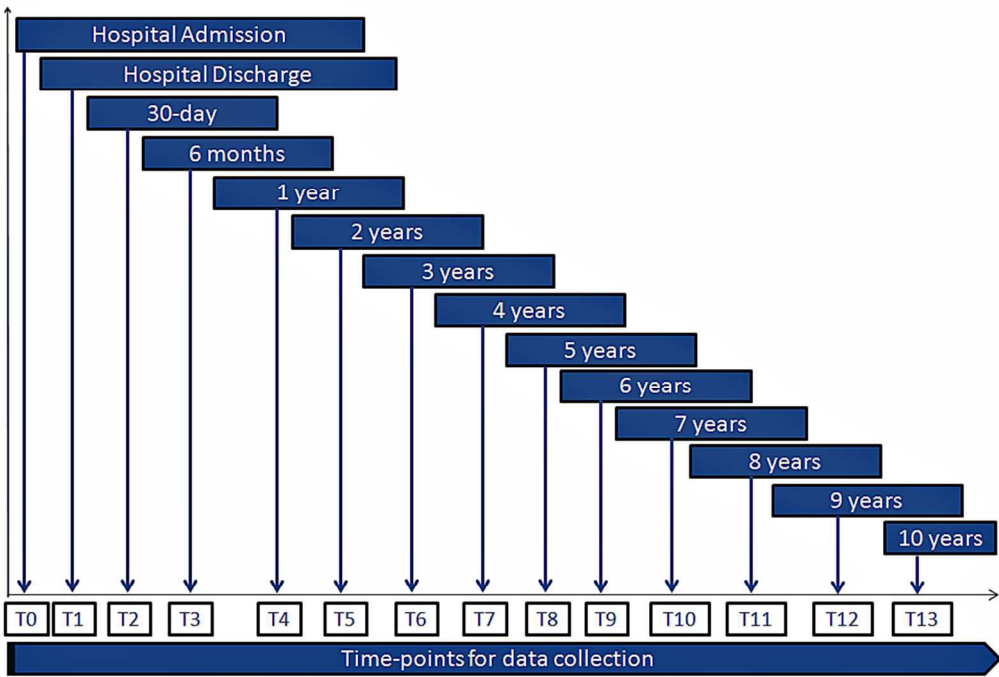
VII. During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?

1
2
3 Not at all Slightly Moderately Quite a lot Extremely
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5 VIII. During the past 4 weeks, how much did personal or emotional problems keep you from
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7 doing your usual work, school or other daily activities?
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9 Not at all Very little Somewhat Quite a lot Could not do daily activities
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Flowchart of enrolment criteria and surgical techniques considered in the registry (CAD: coronary artery disease)

81x56mm (300 x 300 DPI)



Flowchart of time-points for data collection

81x56mm (300 x 300 DPI)

Appendix. E-AVR Collaborators

1. **Tiziano Gherli, MD** – Div. Cardiac Surgery, University of Parma, Parma, Italy
2. **Giuseppe Faggian, MD** and **Livio San Biagio, MD** – Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy
3. **Aung Oo, MD PhD** and **Rakesh Uppal, MD PhD** - Division of Cardiac Surgery, St. Barth Hospital NHS, London, UK
4. **Francesco Musumeci, MD** – Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy
5. **Hermann Reichenspurner, MD** – Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany
6. **Manuel Castellà, MD** – University Hospital Clinic, Barcellona, Spain
7. **Antonio Salsano, MD** – Cardiac Surgery Unit, University of Genova, Genoa, Italy
8. **Alessandro Della Corte, MD PhD** and **Ciro Bancone, MD** - Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy
9. **Ugolino Livi, MD** - Cardiothoracic Department, University Hospital of Udine, Udine, Italy
10. **Nicola Masala, MD** and **Gavin J. Murphy, MD** - Department of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK
11. **Sidney Chocron, MD PhD** - Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France
12. **Giuseppe Gatti, MD** and **Luca Maschietto, MD** - Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy
13. **Stefano Salizzoni, MD** – Dpt of Cardiac Surgery, Torino University Hospitals, Turin, Italy
14. **Francesco Pollari, MD** - Cardiovascular Center, Klinikum Nürnberg – Paracelsus Medical University, Nuremberg, Germany

15. **Alessandro Di Cesare, MD** - Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN,
Hopital Robert Debre', Reims, France

16. **Giulia Bisoffi, PhD**, Unit for Clinical Research and Biostatistics, Verona University
Hospital, Verona, Italy

For peer review only

SPIRIT CHECKLIST

1. Outcomes comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)
2.
 - a. ClinicalTrials.gov # NCT03143361
 - b. WHO Dataset specifications:
 - i. European Aortic Valve Registry (E-AVR); protocol n. 1
 - ii. Registration date: May 3, 2017
 - iii. ClinicalTrials.gov # NCT03143361
 - iv. Fundings: none
 - v. University of Parma, Parma, Italy
 - vi. None
 - vii. Prof. Francesco Nicolini, Div. Cardiac Surgery, University of Parma, Parma, Italy; email: francesco.nicolini@unipr.it; Via A. Gramsci 14 – 43126 - Parma (PR) – Italy
 - viii. Prof. Francesco Nicolini, Div. Cardiac Surgery, University of Parma, Parma, Italy; email: francesco.nicolini@unipr.it; Via A. Gramsci 14 – 43126 - Parma (PR) – Italy
 - ix. Dr. Francesco Onorati, Div. Cardiac Surgery, University Hospitals in Verona, Verona, Italy; email: francesco.onorati@aovr.veneto.it; Piazzale Stefani, 1 – 37100 - Verona (VR) – Italy
 - x. European Aortic Valve Surgery Registry
 - xi. Outcome comparison of different surgical strategies for the management of severe aortic valve stenosis: study protocol of a prospective multicentre European registry (E-AVR Registry)
 - xii. Italy, United Kingdom, France, Germany, Spain, Switzerland
 - xiii. Surgical treatment of aortic valve stenosis with or without concomitant coronary artery disease
 - xiv. The following interventions will be analyzed:
 1. Surgical Aortic Valve Replacement (SAVR) via:
 - a. Full Sternotomy
 - b. Mini-thoracotomy
 - c. Mini-sternotomy
 - d. Stented prostheses (mechanical and biological)
 - e. Stentless prostheses (biological)
 - f. Sutureless prostheses (biological)
 2. Surgical Transcatheter Aortic Valve Replacement (TAVR) via:
 - a. Mini-thoracotomy via trans-apical route
 - b. Mini-sternotomy via trans-aortic route
 - c. Mini-thoracotomy via trans-aortic route
 - d. Sub-clavear via trans-axillary route
 - xv. Inclusion criteria: Isolated severe aortic valve stenosis (SAVS) with or without concomitant aortic valve regurgitation; isolated prosthetic aortic dysfunction; SAVS + coronary artery disease (CAD); prosthetic aortic dysfunction + CAD; age >18 yy; elective, urgent and emergent procedures; endocarditic aetiology; exclusion criteria: concomitant mitral valve surgery, tricuspid valve surgery, aortic surgery, atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG); surgical aortic annular enlargement; porcelain aorta; pure aortic valve regurgitation; percutaneous TAVR; patient refusal
 - xvi. Prospective non-randomized open cohort study
 - xvii. 1st November, 2017
 - xviii. A minimum of 8000 patients in 2 years of enrolment
 - xix. Waiting for the start of enrolment
 - xx. All-cause mortality (any death, either of cardiovascular and non cardiovascular nature) at 5 year from enrolment. Checked by linking with regional Social Security Death and Events Master files, by phone contact with general practitioner, and in case of absent/missing data by direct phone contact with families.

xxi.

1. *All-cause mortality* (any death, either of cardiovascular and non cardiovascular nature) at 30-day, 6-month, 1-year and yearly up to 10-year (5-year excluded) follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with families.
2. *Cardiovascular mortality* (the sum of: 1) death due to proximate cardiac cause, e.g. myocardial infarction, cardiac tamponade, worsening heart failure, low cardiac output syndrome, etc.; 2) death caused by non-coronary vascular conditions, e.g. pulmonary embolisms, stroke, aortic rupture or vascular dissection, etc; 3) all procedure-related deaths, including those related to a complication of the procedure or a treatment for a complication of the procedure; 4) all valve-related deaths including valve dysfunction - structural or non-structural - and other valve-related adverse events; 5) sudden or unwitnessed death) at 30-day, 6-month, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with families.
3. *30-day Type 5 myocardial infarction*: defined according to the recent criteria defined by Moussa et al. (J Am Coll Cardiol 2013; 62:1563-1570). Assessed at 30-day. Collected from hospital registries.
4. *30-day stroke*: classified as 1) ischemic; 2) haemorrhagic; 3) unknown, according to VARC-2 consensus (Eur J Cardio Thorac Surg 2012; 42: S45–S60). The diagnosis and nature of stroke will be supported by CT or MRI imaging and confirmed by a consultant neurologist. Assessed at 30-day. Collected from hospital registries.
5. *Early repeated intervention for index intervention failure*: This refers to any surgical or percutaneous procedure on the aortic valve and/or the coronary arteries, performed during the same hospital stay for any prosthesis-related or graft-related complication. These events will be marked as occurring or not, and further detailed in their nature (“valvular early procedure”, “coronary early procedure” or “coronary + valvular early procedure”). Further details will be collected as explanatory notes. Assessed at 30-day. Collected from hospital registries.
6. *Postoperative need for prolonged use of inotropes*: this refers to the use of inotropes for >72 hours after the index operation. The type, dose and duration of administered inotropes will be also collected. Assessed at 30-day. Collected from hospital registries.
7. *Need for intra-aortic balloon pump (IABP)*: intra- or postoperative insertion of an intra-aortic balloon pump device. Assessed at 30-day. Collected from hospital registries.
8. *Need for extracorporeal mechanical oxygenation (ECMO)*: intra- or postoperative insertion of an extracorporeal mechanical pump/oxygenation device. Assessed at 30-day. Collected from hospital registries.
9. *Surgical site infection*: wound complications are graded according to the Centre for Disease Control and Prevention definitions of surgical site infections (Infect Control Hosp Epidemiol 1999; 20: 250-278). Any surgical site infection occurring within three months after surgery will be considered as a postoperative wound infection. Assessed at 30-day and 3 months after procedure. Collected from hospital registries and outpatient clinic registries.
10. *Bleeding*: classified as 1) life-threatening or disabling bleeding; 2) major bleeding; 3) minor bleeding, according to the recent definition criteria reported by the VARC-2 document (Eur J Cardio Thorac Surg 2012; 42: S45–S60). Assessed at 30-day. Collected from hospital registries.

11. *Blood losses at 12 hours*: the amount of postoperative blood losses from mediastinal drainages 12 hours after surgery. Intraoperative blood losses are not taken into account. Nadir haemoglobin and nadir haematocrit will be collected. Assessed at 30-day. Collected from hospital registries.
12. *Use of blood products during hospitalization for the index surgical procedure*: total amount of blood products (detailed as red packed cells, fresh frozen plasma, or platelet concentrates) from the beginning of surgery to the day of discharge. Assessed at 30-day. Collected from hospital registries.
13. *Resternotomy for bleeding*: Any reoperation for postoperative bleeding, regardless of concomitant hemodynamic problems. Assessed at 30-day. Collected from hospital registries.
14. *Pericardial effusion requiring treatment*: any pericardial effusion requiring interventional treatment (e.g. pericardiocentesis, subxifoid drainage, resternotomy, etc) due to cardiac tamponade, sub-tamponade, or hemodynamic instability refractory to conservative treatment-strategies. Assessed at 30-day. Collected from hospital registries.
15. *Acute renal failure*: severity of acute renal failure after surgery will be graded in AKIN stages from 1 to 3, according to VARC-2 criteria (Eur J Cardio Thorac Surg 2012; 42: S45–S60). Assessed at 30-day. Collected from hospital registries.
16. *Atrial fibrillation*: any new paroxysmal/permanent atrial fibrillation episode requiring or not requiring pharmacological or electrical cardioversion attempts. Number of recurrences will be also collected. Assessed at 30-day. Collected from hospital registries.
17. *Cardiac conduction disturbances*: defined as a new left bundle branch block, right bundle branch block, or AV-block (1st, 2nd or 3rd degree). Diagnosis will be based on official medical reports from a consultant cardiologist. In case of progressive bradi-arrhythmias, the evolution of the arrhythmias will be collected. Assessed at 30-day. Collected from hospital registries.
18. *Need for permanent PMK*: collected as a dichotomic variable. Type of permanent pacing set-up (e.g. AAI, VVI, DDD, etc) will be collected. Assessed at 30-day. Collected from hospital registries.
19. *Length of stay in the intensive care unit*: number of hours spent in the intensive care unit from surgery. Readmissions to intensive care unit will be considered and included in the number estimation. Assessed at 30-day. Collected from hospital registries.
20. *Length of in-hospital stay*: number of days spent into hospital (ICU-stay will be added) from the day of surgery to hospital discharge to any other hospital ward, rehabilitation unit or home. Assessed at 30-day. Collected from hospital registries.
21. *Follow-up stroke*: any focal or global neurological syndrome occurring after discharge and caused by ischemia and/or haemorrhage not resolving within 24 hours. The diagnosis and nature of stroke will be made on the basis of findings from brain CT, or MRI, or based on the medical report of a consultant neurologist. Assessed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
22. *Follow-up myocardial infarction*: any myocardial infarction occurring after discharge and requiring medical, interventional or surgical treatment occurring after discharge. Assessed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by

- phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
23. *Follow-up re-intervention on the aortic valve*: re-intervention is defined as any surgical or percutaneous interventional treatment that replaces (or repairs) an aortic prosthesis implanted at the time of the index procedure which is dysfunctional for either structural or non-structural reasons. Analyzed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
24. *Follow-up aortic valve-related adverse event*: this includes: 1) embolism; 2) valve thrombosis; 3) bleeding events; 3) structural valve deterioration; 4) paravalvular leakage; 5) operated valve endocarditis; 6) haemolysis, based on the definitions of current Guidelines for reporting mortality and morbidity after cardiac valve interventions (J Thorac Cardiovasc Surg 2008; 135: 732-8). Analyzed at 30-days, 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
25. *Follow-up repeated revascularization*: any CABG and/or PCI performed after discharge for coronary graft dysfunction and/or valve-related coronary complication. Any revascularization due to the progression of an untreated subcritical (at the time of the index procedure) coronary target will not be considered. Analyzed at 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
26. *Composite outcome*: according to VARC-2 definitions (Eur J Cardio Thorac Surg 2012; 42: S45–S60), this includes: 1) device success (absence of procedural mortality with correct positioning of a single prosthesis and with intended performance of the prosthesis); 2) early safety at 30 days (composite endpoint of all-cause mortality, all strokes, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary obstruction requiring intervention, major vascular complication or valve-related dysfunction requiring repeat procedure); 3) clinical efficacy after 30 days (composite endpoint of all-cause mortality, all strokes, hospitalization for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV, valve related dysfunction); 4) time-related valve safety (composite endpoint of structural valve deterioration requiring repeat procedure, prosthetic valve endocarditis, thrombosis, thrombo-embolic events or valve-related VARC bleeding). Analyzed at 30-days, 6-months, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with patients and/or families.
27. *MACCE* (defined as composite end-point including any of the following adverse events: death from cardiovascular cause, stroke, myocardial infarction, repeated revascularization) at 30-day, 6-month, 1-year and yearly up to 10-year follow-up. Checked by linking with hospital and outpatient clinic registries, with regional Social Security Death and Events Master files, or by phone contact with general practitioner; in case of absent/missing data by direct phone contact with families.

28. Quality of life (QoL; defined according to Short Form-8 questionnaire) at hospital admission, at 30-day, 6-months, 1-year and yearly up to 10-year follow-up. QoL will be assessed during follow-up visits at outpatient clinics or, if other methods are not possible, by telephone interview.
 29. Echocardiographic data of prosthesis performance. Data collected at echocardiographic examination are based on VARC-2 criteria (37). A minimum set of echocardiographic data will be considered: 1) left ventricular (LV) function (EF% based on Simpson's method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade (defined as mild, moderate or severe based on several different echocardiographic indexes as regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local institutional policies). Further assessment of "intra-prosthetic", "peri-prosthetic" or "combined intra+peri-prosthetic" regurgitation will be added. Echocardiographic data will be assessed at hospital admission, before hospital discharge, at 30 days after surgery, 6 months, 1 year after implantation, and yearly thereafter up to the follow-up closure (10th year) by Institutional 3rd level certified Echocardiographic Laboratories: 5% of these echocardiographic exams will be reviewed centrally (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) by third level certified echocardiographers.
3. Protocol n.2.2.17 of 1st October, 2017
 4. Funding: None
 5.
 - a. *Francesco Nicolini, MD PhD, Associate Professor.* Div. Cardiac Surgery, University of Parma, Parma, Italy; Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing, member of the E-AVR Steering Committee
 - Francesco Onorati, MD PhD.* Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee
 - Riccardo Gherli, MD.* Div. Cardiac Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee
 - Giovanni Mariscalco, MD PhD.* Dpt. of Cardiovascular Surgery and Anesthesia and Critical Care of Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK; Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee
 - Evaldas Girdauskas, MD.* Dpt. Cardiovascular Surgery University Heart Center Hamburg, Hamburg, Germany, Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee
 - Eduardo Obrador Quintana, MD.* University Hospital Clinic, Barcellona, Spain; Design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Francesco Santini, MD Full Professor. Cardiac Surgery Unit, University of Genova, Genoa, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Marisa De Feo, MD PhD Full Professor. Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Sandro Sponga, MD PhD. Cardiothoracic Department, University Hospital of Udine, Udine, Italy; Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Piergiorgio Tozzi, MD Associate Professor. Cardiac Surgery Unit, Centre Hopitalier Universitaire Vaudois, Lausanne Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Mohammad Bashir, MD. Division of Cardiac Surgery, St. Barth Hospital NHS, London, UK. Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Andrea Perrotti, MD. Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France. Conception and design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Aniello Pappalardo, MD. Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy. Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Vito Giovanni Ruggieri, MD Professor. Chirurgie Thoracique et Cardio-Vasculaire, Pole TCVN, Hopital Robert Debre', Reims, France; Conception of the study, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Giuseppe Santarpino, MD. Cardiovascular Center, Klinikum Nürnberg – Paracelsus Medical University, Nuremberg, Germany. Drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspects of the study, member of the E-AVR Steering Committee

Mauro Rinaldi, MD PhD Full Professor. Department of Cardiac Surgery, Torino University Hospitals, Turin, Italy. Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee

Carlo Antona, MD Full Professor. Department of Cardiac Surgery, Ospedale Sacco, Milan, Italy; Conception of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee.

Silva Ronaldo Rouvher Guedes, PhD, Biostatistician. Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy. Design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing

Tiziano Gherli, MD Full Professor. Div. Cardiac Surgery, University of Parma, Parma, Italy; Conception of the study, design of the study, database building, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, ClinicalTrials.gov publishing, member of the E-AVR Steering Committee

Giuseppe Faggian, MD PhD Full Professor. Div. Cardiac Surgery, University of Verona Medical School, Verona, Italy; Conception of the study, design of the study, drafting the paper, critically revising the paper, final approval of the version to be published, agreement to be accountable for all aspect of the study, member of the E-AVR Steering Committee.

- b. Prof. Francesco Nicolini, Div. Cardiac Surgery, University of Parma, Parma, Italy; email: francesco.nicolini@unipr.it; Via dell'Università n.12 – 43121 - Parma (PR) – Italy.
- c. Funders: None. Sponsor roles: no external sponsor for the trial. The PI (Prof. F. Nicolini) has active participation in study design, collection and management of data (analysis of data performed by an external Statistical Core Laboratory), interpretation of data, writing reports, and decision to submit the reports for publication; however, no ultimate Authority over any of these activities
- d. Coordinating Centre composition: Professor Francesco Nicolini, MD, and Professor Tiziano Gherli, MD; Div. Cardiac Surgery University of Parma. Roles: coordination of the Registry, active participation in study design, collection and management of data (analysis of data performed by an external Statistical Core Laboratory), interpretation of data, writing reports, and decision to submit the reports for publication. No ultimate Authority over any of these activities. Responsibility: coordination of the Registry, E-AVR Steering Committee adherence to its roles.
Steering Committee: Composition: F. Onorati, F. Nicolini, R. Gherli, G. Mariscalco, E. Girdauskas, E.O. Quintana, F. Santini, M. De Feo, S. Sponga, P. Tozzi, M. Bashir, A. Perrotti, A. Pappalardo, V.G. Ruggieri, G. Santarpino, M. Rinaldi, C. Antona, Silva RRG, T. Gherli, G. Faggian.
Roles: Generate the sequence to maintain anonymized the entire set of data, protect confidentiality about patient identity before, during and after the trial, and retain data in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.
Take responsibility of data collection, data monitoring through local auditing, endpoint analysis, and writing process; evaluation of sub-study proposal from researchers involved in the Registry, and accept/reject it by vote after review and discussion about its feasibility; take any decisions on co-authorship on the basis of individual contribution to the design of the study, data collection, interpretation of data, writing, and critical review of the paper; establish periodical E-AVR Steering Committee meetings; maintain a copy of the complete database.
Take responsibility of further checking, reviewing, correcting and merging in case of incomplete or contradictory data, and in case of data without identification code.
Data Management: apart from a local data auditing (responsibility of the E-AVR Steering Committee), the Central Core Statistical Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) will centrally adjudicate clinical outcome data, and take responsibility of storage, analysis and auditing of data every six-months. Furthermore, 5% of echocardiographic data will be reviewed centrally (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy) by third level certified echocardiographers

6.

- a. The prevalence of severe aortic valve stenosis (SAVS) correlates with age, and its treatment is expected to increase parallel to the improved life-expectancy reported in Western Countries (1-2). Traditional surgical aortic valve replacement (SAVR) has been the gold standard of treatment for decades, with well-documented benefits in terms of symptom improvement and survival (3-4). Recent technological advances allowed interventional and surgical transcatheter aortic valve replacements (TAVR), which proved to be effective alternatives to traditional SAVR, in both high-risk and intermediate-risk patients (5-12). Therefore, SAVR and TAVR represent nowadays the standard surgical armamentarium for aortic valve replacement. Alternative surgical approaches, based on the concept of TAVR (13,14), have in fact been developed. There are on the market two types of “sutureless” valves (i.e. Sorin Perceval and Edwards Intuity) at the moment - aimed at reducing some surgical drawbacks such as cross-clamp time and myocardial ischemia-reperfusion injury

(13,15-20) – but it is possible that new “sutureless” valves will enter the market in the next future. Moreover, different mini-thoracotomy and mini-sternotomy approaches to SAVR have been widely adopted by the surgical community - with both “sutured” and “sutureless” valves - in order to reduce surgical trauma, systemic inflammatory response, and major organ morbidity (13,15,16). Various different combinations of minimally invasive accesses and the use of last-generation valves have been reported to date (14,17,18). But despite early enthusiasm about preliminary results with these technological improvements, none of these techniques has yet replaced traditional SAVR in standard surgical practice, mainly because reporting of results of these alternative techniques tends to be biased by single-centre design, limited sample-size, and the strict inclusion/exclusion criteria of the published studies (13,14).

Another “hot topic” in this debate relates to valve durability, given that the long-term durability of both TAVR and sutureless valves is as yet unknown. Indeed, standard “sutured” surgical valves demonstrated excellent durability, both in the very-long term and in very-young adults below the 65-year cut-off age (21-23), which is still the threshold for biological valves recommended by European Society of Cardiology (ESC) / European Association for CardioThoracic Surgery (EACTS) guidelines (24). This issue is of particular interest, given that the use of TAVR has increased in younger intermediate-risk patients, despite recent caveats relating to early degeneration of TAVR (25,26).

Similarly, improved life-expectancy has led to a growing number of patients with degenerated dysfunctioning aortic bioprostheses requiring surgical treatment. Again, surgical aortic prosthetic replacement (SAPR) has been traditionally considered the only treatment strategy for these patients, given the excellent results, recently confirmed by several studies (27,28). Again, transcatheter treatments (“valve-in-valve”) have recently demonstrated comparable or sometimes superior results in redo-scenarios (29). Therefore, data on the efficacy, safety and durability of these technological improvements are essential for providing “strong” statements in future guidelines, and for evaluating the extension of these techniques to low-risk and young patients in the future.

Finally, it is well known that critical coronary artery disease (CAD) often coexists with SAVS. Although the standard treatment option for these patients has traditionally been SAVR plus coronary artery bypass grafting (CABG), the introduction of TAVR and minimally invasive surgical alternatives has considerably changed the available options, paving the way to combined less-invasive SAVR+CABG and/or TAVR±PCI (either before, during or after the surgical procedure) (30-34). Again, there is a great deal of confusion on the topic, and there are unanswered questions on the efficacy and safety of these options, as well as on what to expect from late follow-up when compared to the standard practice of SAVR+CABG.

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- b. Robust early and follow-up data on the safety and efficacy of surgical TAVR, last-generation sutureless surgical valves, and minimally-invasive approaches compared with standard SAVR, with or without a contemporary (surgical or interventional) treatment of concurrent CAD, are still lacking for a real-world large population of patients at variable surgical risk. Such data is urgently required for the correct allocation of therapy in daily surgical practice. Furthermore, data on quality of life and functional echocardiographic results with different surgical alternatives might similarly help physicians in decision-making in local "Heart Teams". Data from a multicentre, real-world, open registry enrolling all patients with SAVS±CAD consecutively referred to several Centres at different European latitudes should help to answer some of these open questions.
In particular, comparative analyses between mid-to-long term outcome of SAVR vs surgical TAVR will clarify the mid-to-long term prognosis associated with these 2 different techniques (risk of death, risk of reintervention, functional class, quality of life, etc)
Comparison between sutured and sutureless aortic prostheses, since hospitalization to 10-year follow-up, will elucidate if (and how much) the use of rapid-deployment valves is superior compared to standard techniques
Comparisons of minimally invasive approaches and full-sternotomy, since hospitalization to 10-year follow-up, will define the safety and efficacy of the former over the latter techniques.
7. The principal objective of the study is the 5-year comparison between outcome after SAVR and outcome after surgical TAVR: we hypothesize to report a 10% superiority in terms of all-cause mortality in favor of SAVR vs. TAVR.
8. The trial is a prospective registry-based observational cohort study, enrolling all patients fulfilling inclusion criteria (all comers), aimed at a superiority design (10% superiority of SAVR vs. TAVR in 5-year all-cause mortality)
9. Settings: University hospitals and 3rd level community hospitals (France, Germany, Italy, Spain, Switzerland, United Kingdom).
10. Inclusion criteria: Isolated severe aortic valve stenosis (SAVS) with or without concomitant aortic valve regurgitation; isolated prosthetic aortic dysfunction; SAVS + coronary artery disease (CAD); prosthetic aortic dysfunction + CAD; age >18 yy; elective, urgent and emergent procedures; endocarditic aetiology. Exclusion criteria: concomitant mitral valve surgery, tricuspid valve surgery, aortic surgery, atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG); surgical aortic annular enlargement; porcelain aorta; pure aortic valve regurgitation; percutaneous TAVR; patient refusal.
Individuals who will perform the interventions: surgeons
11.
 - a.

Surgical aortic valve replacement (SAVR) with any of the following surgical accesses:

- i. Full sternotomy
- ii. Mini-thoracotomy
- iii. Mini-sternotomy

And with any of the following prostheses:

- i. Mechanical prostheses
- ii. Biological stented prostheses
- iii. Biological stentless prostheses
- iv. Biological sutureless prostheses

OR

Surgical Transcatheter valve replacement (TAVR) with any of the following surgical accesses:

- iv. Mini-thoracotomy via trans-apical route
- v. Mini-sternotomy via trans-aortic route
- vi. Mini-thoracotomy via trans-aortic route
- vii. Sub-clavear via trans-axillary route

SAVR will be performed always under cardiopulmonary bypass. TAVR will be administered on the beating heart or, rarely, under cardiopulmonary bypass or extracorporeal circulation and membrane oxygenation according to the clinical scenario and Heart Team choice (e.g. severe hemodynamic compromise avoiding the possibility to perform TAVR with a standard unassisted beating heart technique). All these strategies are administered the day scheduled for surgical intervention.

- b. Criteria for discontinuing, withdrawing or modifying allocated intervention: intraoperative demonstration of unexpected porcelain aorta; unplanned need for concomitant mitral valve surgery, and/or tricuspid valve surgery, and/or aortic surgery, and/or atrial fibrillation surgery, and/or any other associated cardiac surgical procedure (with the exception of CABG); unplanned need for a surgical aortic annular enlargement
- c. N.A.: there are no strategies to improve adherence to protocols: this because any intraoperative and postoperative strategy/protocol is allowed (observational nature of the study), and then recorded in the Registry.
- d. Concomitant interventions that are prohibited during the trial are: planned concomitant mitral valve surgery, tricuspid valve surgery, aortic surgery, atrial fibrillation surgery, or any other associated cardiac surgical procedure (with the exception of CABG); planned surgical aortic annular enlargement.

Given the observational nature of this prospective registry-based cohort study, all the possible concomitant medical strategies of the daily care are allowed and reported in the registry.

12. Primary outcome:

- i. 5-year all-cause mortality (time to event; proportion; 5-year time-point)

Secondary outcomes:

- ii. Cardiovascular mortality (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- iii. All-cause mortality (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- iv. Type 5 myocardial infarction (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- v. Stroke (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points)
- vi. Early repeated intervention for index intervention failure (time to event; proportion; 30-day).
- vii. Postoperative need for prolonged use of inotropes (final value; proportion; 30-day time-point)
- viii. Need for intra-aortic balloon pump (time to event; proportion; 30-day time-point)
- ix. Need for extracorporeal mechanical oxygenation (time to event; proportion; 30-day time-point)
- x. Surgical site infection (time to event; proportion; 30-day and 6-month time-points)
- xi. Bleeding (final value; proportion; 30-day time-point)

- xii. *Blood losses at 12 hours* (final value; proportion; 30-day time-point)
- xiii. *Use of blood products during hospitalization for the index surgical procedure* (final value; proportion; 30-day time-point)
- xiv. *Resternotomy for bleeding* (time to event; proportion; 30-day time-point)
- xv. *Pericardial effusion requiring treatment* (time to event; proportion; 30-day time-point)
- xvi. *Acute renal failure* (time to event; proportion; 30-day time-point)
- xvii. *Atrial fibrillation* (time to event and final value; proportion; 30-day time-point)
- xviii. *Cardiac conduction disturbances* (time to event; proportion; 30-day time-point)
- xix. *Need for permanent PMK* (time to event; proportion; 30-day time-point)
- xx. *Length of stay in the intensive care unit* (final value; proportion; 30-day time-point)
- xxi. *Length of in-hospital stay* (final value; proportion; 30-day time-point)
- xxii. *Follow-up re-intervention on the aortic valve*: (time to event; proportion; 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxiii. *Follow-up aortic valve-related adverse event* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point).
- xxiv. *Follow-up repeated revascularization* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxv. *Device success* (time to event; proportion; 30-day)
- xxvi. *Early safety at 30 days* ((time to event; proportion; 30-day)
- xxvii. *Clinical efficacy after 30 days* (time to event; proportion; 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxviii. *Time-related valve safety* (time to event; proportion; 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxix. *MACCE* (time to event; proportion; 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxx. *Quality of life* (change from baseline; median; hospital discharge, 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)
- xxxi. *Echocardiographic data of prosthesis performance* (change from baseline; median; hospital discharge, 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year time-points time-point)

13. 2- year of enrolment, starting on November, 1st 2017 and ending on October 30th 2019; 10-year of follow-up (closure on September 30th 2029). Data collection pertaining the hospital course. Follow-up time points: 30-day, 6-month, 1-year, 2-year, 3-year, 4-year, 5-year, 6-year, 7-year, 8-year, 9-year, and 10-year.

Hospital admission	Hospital course	Discharge	30-day	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8 year	9 year	10 year
Enrollment Baseline data Quality of life (QoF) Echocardiographic parameters (Echo)	Data pertaining surgery and postoperative care. Hospital outcome adjudication	Type of discharge QoF Echo	Outcomes adjudication (O.A.) QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	Primary outcome O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo	O.A. QoF Echo

14. It is intended to enrol 8000 patient, of which 60 to 70% will be SAVR and the remainder TAVR (historical data based on Institutional practices). Considering the estimated event rate of 25% in the TAVR patients at 5 years (36), a 2-year accrual time, an anticipated loss-to-follow-up rate of 1.5% (historical data), and the target power of 80% at a 0.05 one-sided log-rank test significance level to detect the hypothesized 10% inferior (absolute improvement) 5-year all-cause mortality rate in favour of SAVR, the calculations showed the overall sample size of the registry to meet the targeted power for all expected scenarios of estimated proportions of SAVR and TAVR patients..
15. This is an all-comers registry-based cohort study. Historical data from the participating Centres demonstrate that at least 8000 patients (far beyond the number requested by sample size calculation) will be collected in 2 years, using an “all-comers” strategy
16. N.A.
17. N.A.
- 18.

- a. Data will be prospectively collected in a dedicated Database. Data pertaining hospitalization will be collected by hospital registries, whereas variables and outcome events occurring after the index hospital discharge will be collected from outpatient clinics at the individual Institutions, and linking with regional Social Security Death and Events Master files. Events and outcome variables will be adjudicated adjudicated centrally by a Central Core Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy). In the event of controversy on outcome adjudication, the outcome will be adjudicated after a final consult between the Central Core Laboratory and the E-AVR Steering Committee. Collection of data is under the responsibility of the Steering Committee local member at each participating Centre.
- Data will be audited from the Central Core Laboratory on a regular basis, as reported previously. In case of absent/missing data, variables and events will be collected by direct phone contact with general practitioners, and only if persistently missed by phone contact with patients and families.
- The Local E-AVR Steering Committee member is responsible for a continuous active auditing of local data. The Central Core Statistical Lab will perform 6-month external auditing by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator and E-AVR Steering Committee for further data checking and merging. Incomplete or contradictory data with patient identification code will be sent from Central Core Statistical Lab to the E-AVR Steering Committee local member for further data checking, review, correction and merging.

Laboratory parameters: baseline levels of haemoglobin, haematocrit, platelets, blood glucose, HbA1c, C-reactive protein, TT-INR, creatinine, e-GFR and albumin will be collected.

Units of measurement: Laboratory data will be collected according to fixed units of measurement in order to avoid any problem stemming from differences in units used by the various participating centres, during data merging and analysis. The fixed units of measurement are reported in the dedicated CRF datasheet.

Short-Form 8 SF-8 Health Survey questionnaire: will be based on eight questionnaire items reported in Table 4 of the protocol.

Echocardiographic data: Data collected at echocardiographic examination are based on VARC-2 criteria (Eur J Cardio Thorac Surg 2012; 42: S45–S60). A minimum set of echocardiographic data will be considered: 1) left ventricular (LV) function (EF% based on Simpson’s method); 2) Indexed LV end-diastolic and end-systolic volumes and diameters; 3) Wall motion score index; 4) Indexed Left atrial volume; 5) Indexed left ventricular mass; 6) native valve and prosthetic valve stenotic indexes (peak velocity, mean gradient, Doppler-velocity index, effective orifice area, indexed effective orifice area), 7) native valve and prosthetic valve regurgitation grade (defined as mild, moderate or severe based on several different echocardiographic indexes as regurgitant volume, regurgitant fraction, effective regurgitant orifice area, etc. based on local institutional policies). Further assessment of

“intra-prosthetic”, “peri-prosthetic” or “combined intra+peri-prosthetic” regurgitation will be added.

- b. Active explanation to patients and families about the importance of adherence to follow-up visits for final interpretation of data – with its consequences on Guidelines and current daily practice - will be pursued.

It is expected that linking with regional Social Security Death and Events Master files and using phone contacts with general practitioners will lead to ascertain at least the following follow-up outcome data: 1) All-cause mortality and cardiovascular mortality; 2) MACCE; 3) Reinterventions on the aortic valve; 4) Valve-related adverse events; 5) Repeated revascularization; 6) Clinical efficacy after 30-days; 7) Time-related valve safety.

On the opposite, it is expected a 100% completeness of data related to hospitalization.

19. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Country (2 letters), enrolling Centre (2 letters), and then consecutive number (considered at thousands)(e.g. Mr. XY, third patient enrolled in London = UKLO0003). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, the external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity.

The Central Core Statistical Laboratory analyzing the data will be blinded towards the surgical teams. The Central Core Statistical Laboratory will take responsibility of data managing. Data will be audited from the Central Core Laboratory on a regular basis, as reported previously. All data will be retained in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.

See “Data Management and monitoring” paragraph of the protocol.

- 20.

- a. Continuous variables will be reported as mean and standard deviation or median and interquartile range, as appropriate. Dichotomous and nominal variables will be reported as counts and percentages. Univariate analysis will be performed using the Mann-Whitney U test and Student’s t-test for continuous variables (pending the not-normal or normal distribution respectively), the Kruskal-Wallis test (independent multilevel ordinal variables), Wilcoxon test (for paired variables), Fisher exact test and Chi-square test (for dichotomous/nominal variables) and Kaplan-Meier test (for time-dependent dichotomous variables). Multivariable analyses will be performed using logistic regression method (for categorical dependent variable), classification tree analysis (for target variables with a discrete set of value), linear regression (for continuous dependent variable) and ordinal regression methods (for ordinal dependent variable), as well as Cox-proportional hazards method (to test the effects of covariates on time-dependent dichotomous variables). Significant differences between study groups will be adjusted by using propensity score as covariate or by one-to-one propensity score matching. Matching will be performed using a caliper width of 0.2 of the standard deviation of logit of the propensity score.
- b. Multiple propensity score adjusted analysis will be performed in case of multiple study groups. A Bayesian hierarchical approach will be used in the case of significant variability between centres. Sensitivity analysis will be executed using complete-case analysis. Interim analyses are planned at different time-points (see Ethics and Dissemination), with critical p-values corrected according to the Armitage-McPherson adjustment
- c. Missing values will be replaced and estimated using multiple imputations.

- 21.

- a. Data Monitoring Committee is not needed because the E-AVR Steering Committee and the Central Core Statistical Lab will take responsibilities of DMC. In particular, data will be collected into a dedicated datasheet with predefined variables. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Country (2 letters), enrolling Centre (2 letters), and then consecutive number (considered at thousands)(e.g. Mr. XY, third patient enrolled in London = UKLO0003). It is

responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity. All data will be retained in a secure location at each study-site during the conduct of the study and for the 5-years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. The E-AVR Steering Committee local member has also the responsibility for a continuous auditing of local data, by double-checking and monitoring of data quality and their completeness. Storage, analysis and further auditing of data will be then accomplished by the independent Central Core Laboratory (Unit for Clinical Research and Biostatistics, Verona University Hospital, Verona, Italy). External auditing of the dataset will be performed every six months by checking the data of a minimum of 40% of the patients. Data without any patient identification code will be submitted to the Principal Investigator and E-AVR Steering Committee for further data checking and merging. Incomplete or contradictory data with patient identification code will be sent from Central Core Statistical Lab to the E-AVR Steering Committee local member for further data checking, correction and merging. Both the E-AVR Steering Committee (with its members) and Central Statistical Core Lab are free from competing interests (the trial has no sponsor).

- b. The following interim-analyses have been established:
1. A 3-year outcome study comparing different surgical techniques of TAVR (i.e. trans-apical vs. trans-aortic vs. trans-axillary approach); propensity-matching and risk-adjusted analyses will be executed if baseline differences are identified between the 3 subpopulations; post-hoc statistical analyses will identify outcome-differences between the 3 subgroups
 2. An interim-study analyzing 30-day outcome of the first 4000 patients enrolled.
 3. A study analyzing 30-day and 1-year outcome of the first 4000 SAVR-patients enrolled. Sub-group analyses will be aimed at compare different surgical accesses (i.e. sternotomy vs. mini-sternotomy vs. mini-thoracotomy); propensity-matching, risk-adjusted and post-hoc analyses will be done appropriately to nullify potential bias in the interpretation of the results, and to compare the results of each surgical subgroup.

The results of these interim analyses will be available to all the E-AVR Investigators for data interpretation, with the aim to write “dedicated” scientific papers on these 3 topics. Given that these 3 interim-analyses do not deal with the primary objective of the registry (5-year outcome comparison between SAVR and TAVR), all these results will not have any impact on the possible termination of the trial. Furthermore, investigated treatments (SAVR and TAVR) are standards of care according to Current Guidelines and Good clinical practice, therefore no stopping guidelines for the premature termination of the trial can be foreseen at the moment.

22. N.A.: the trial is an observational registry-based cohort study, with collection of data representing standard surgical practice and state-of-the-art perioperative care for cardiac surgical interventions. There are no randomized interventions nor treatments administered per-protocol, therefore no “adverse events” or “unintended effects” directly related to the conductance of the trial can be foreseen.
23. The Local E-AVR Steering Committee local member is responsible for a continuous active auditing of local data. The Central Core Statistical Lab will perform 6-month external auditing – independent from investigators (no sponsor exists) - by checking the data of a minimum of 40% of the patients.
24. All Ethical Committee (EC) approvals (from the PI Centre, University of Parma, and from satellite centres) have been obtained.
25. Important protocol modifications will be discussed inside the E-AVR Steering Committee and -if accepted – communicated to all the E-AVR investigators, as well as to all the ECs of the E-AVR participating Centers by means of “amendment requests”. Only in case of approvals from all ECs the modification will enter the protocol.
- 26.

- a. Written informed consent will be obtained from the patient or patient's authorized representative prior to enrolment in the Registry. In case of emergent surgery, informed consent will be collected from the patient's family (or legal representative) before surgery, as well as from the patient after surgery (if unable to give it before intervention). This consent will be waived in case of death or severe neurological damage precluding adequate postoperative patient informed consent. The study will be conducted in accordance with the provisions of the Declaration of Helsinki.
 - b. N.A.: no ancillary studies are planned
27. Each patient enrolled in the Registry will be anonymized by the generation of a code consisting of the initials of the enrolling Country (2 letters), enrolling Centre (2 letters), and then consecutive number (considered at thousands)(e.g. Mr. XY, third patient enrolled in London = UKLO0003). It is responsibility of the E-AVR Steering Committee local member to generate the sequence to maintain anonymized the entire set of data. It is also responsibility of the E-AVR Steering Committee local member to protect confidentiality about patient identity before, during and after the trial. Accordingly, external Central Statistical Core Lab (as well as all the other E-AVR investigators) will be blinded towards patient identity. Each participating centre will be anonymized by identification with a capital letter. The correspondence between centres and capital letters will only be known by the PI of the study. The Central Core Laboratory analyzing the data will be blinded towards the surgical teams.
28. No financial and/or competing interests for principal investigators, for the overall trial and each study site
29. The final dataset is only available to the Central Statistical Core Lab. However, the entire sets of the performed statistical analyses of the primary study and of secondary sub-studies will be available to all E-AVR researchers for the clinical interpretation of data. There is the agreement between E-AVR Investigators and Central Statistical Core Lab that preclude the access of final dataset to all the E-AVR Investigators.
30. N.A.: given the observational nature of this prospective registry-based cohort study, no ancillary or post-trial care is scheduled, and no harm is expected from the participation to the registry
- 31.
- a. Research findings from the E-AVR registry will be disseminated among the scientific community. They will be presented at international congresses and published in peer reviewed international journals in the fields of cardiac surgery and cardiology. Any formal presentation or publication of data will be considered as a joint publication by the participating physician(s) and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship. Data collection, analysis and writing process will be monitored by the Steering Committee of the E-AVR, which is made up of the Principal Investigator and a Representing Member from each of the participating centres. It is expected that periodical E-AVR Steering Committee meetings will occur, every 6 months for the first 2 years, yearly thereafter up to the end of follow-up. In the event of future merging with other contemporary registries (e.g. collecting data on concurrent interventional – i.e. percutaneous transfemoral, transcarotid or trans-axillary - TAVR procedures), the co-authorship of comparative studies (e.g. between surgical and interventional treatments) will be defined by the Steering Committees of the different registries involved. However, data will not made available for sharing until after publication of the principal results of the study. Thereafter, anonymized individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed used of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements, and value for money. Anonymized data will be shared as long as the patient has agreed and consented to this. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research.
 - b. Investigators will be eligible for authorship if they contribute substantially to study planning, data collection, data analysis and interpretation, writing and critical review of the manuscripts. Two authors per centre will be included as main authors of each study. As a

- member of the Steering Committee, the local Representing Member will take any decisions on co-authorship related to his/her centre on the basis of the above criteria. Those researchers who plan a sub-study, interpret the analysis and write the article will be the first and last authors of the study. When an article is submitted to a journal with a maximum number of co-authors, the Steering Committee will decide on the authors on the basis of their contribution to the design of the study, data collection, interpretation of data, writing, and critical review of the paper.
- c. No plan for granting public access to the full protocol, participant-level dataset and statistical code has been considered

32. PARTICIPANT INFORMATION LEAFLET

E-AVR: a Prospective European Multicenter Study on Aortic Valve Replacement

Introduction

You are being invited to take part in a clinical research study. However, before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Taking part in research is voluntary and your medical care will not be affected if you decide not to take part.

If anything is not clear or you would like more information, do not hesitate to ask your research doctor or another member of the research team when you come into hospital (also see contact details at the end of this leaflet).

Talk to others about the study if you wish, such as friends or relatives and take time to decide. If you would like to take part, you will be asked to confirm this before your operation, during your admission or at follow-up after discharge by signing a separate consent form.

What is the purpose of the study?

Severe aortic valve stenosis (abbreviation: SAVS) is a life-threatening disease in which the valve is blocked by the progressive degeneration of its tissue. The same situation is encountered some years after the implantation of a biologic aortic prosthesis, due to the progressive inflammation of prosthetic tissues (biologic prosthetic degeneration). Both conditions are usually treated with the replacement of the patient's failing aortic valve (or prosthesis) with an artificial prosthesis (surgical aortic valve replacement, abbreviation: SAVR, and surgical prosthetic valve replacement, abbreviation: SPVR). For decades the standard of care has been represented by performing this surgery through a surgical incision of the entire sternum (sternotomy) and with the aid of the so called heart lung machine (i.e., the heart is arrested during the central part of the operation, and vital functions are sustained with this machine). Recently, new surgical techniques have been developed. Indeed, it is possible to proceed to SAVR via different surgical skin incisions (sternotomy, partial sternotomy, small thoracotomy) but always using heart-lung machine; or it is possible to replace the failing valve with new biological prostheses - crimped on a catheter - implanted on the beating heart through small skin incisions (the latter called transcatheter aortic valve replacement, abbreviation: TAVR).

Native/prosthetic aortic valve replacement is one of the most commonly performed operation in cardiac surgery. Around 100,000 AVR procedures are performed in Europe every year. As with all types of surgery, it carries a risk of complications, usually minor, but there is also a risk of serious complications such as stroke, heart attack or even death. Together with other European centers we want to create a large database (registry) of patients affected by SAVS and undergoing surgical substitution of the failed native/prosthetic aortic valve (named E-AVR Registry) as we think that collection and analysis of data on risk factors, operative techniques, post-operative treatment and secondary prevention strategies will improve treatment and reduce the risk of early and late complications.

Why have I been invited?

You have been invited to take part because you are going to have or you already had an aortic valve replacement. Like you hundreds of patients across Europe will be invited to take part.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide and if you take part you are free to withdraw at any time. If you choose not to take part or to withdraw from the research, you do not have to give any reason for your decision. The operation performed and the care you will receive after will be exactly the same whether you take part in the study or not.

What will happen to me if I take part?

You will be asked to give written consent to take part in the study and you will be given a copy of the consent form and this information leaflet to keep. After discharge we will collect data regarding your pre-operative clinical status, operation and post-operative course. The data collected will be made anonymous prior to be entered into a large European database and shared with other researchers across Europe. Personal identifiable information will not be shared and will remain strictly confidential.

What are the possible disadvantages and risks of taking part?

We do not think that taking part in the study will expose you to any risks or disadvantages. You may be contacted in the future and asked a number of questions regarding your health as a result of cardiac surgery.

What are the possible benefits of taking part?

We think that the information from this research will help us to improve treatment and ameliorate the early and late outcomes for patients having aortic valve replacement (AVR) in the future.

What will happen to the results of the study?

The results of the study will be published in medical journals or shared during medical meetings. Thereafter, anonymous individual patient data will be made available for secondary research, after a proper research approval. You will not be identified in any way. If you would like to receive the results of the study written in plain English, after the research has finished, please contact the study team on the numbers provided at the end of this leaflet.

Further information and contact details:

If you have any concerns or questions about this study please contact the research team on the number or email address provided below. Please use the contact details only for questions about the E-AVR study project. Alternatively you can discuss these with a member of the research team who will come to see you before your operation. Please feel free to ask any further questions before deciding to take part in the study, or at any time during it.

Contact details:

If you want further information contact Dr X X (xxxxxxxxxxxxxxxxxx) or email (xxxxxxxxxxxx).

Other members of the Research Team (email):

Dr. X X (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)

Dr. X X (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)

CONSENT FORM

Name of Researcher: Dr X X

Name of the study: E-AVR: a Prospective European Multicenter Study on Aortic Valve Replacement

I have had the opportunity to consider the information provided, ask questions and have had these answered satisfactorily	<input type="checkbox"/>
I understand that my participation in the E-AVR registry is voluntary and that I am free to withdraw at any time, without giving any reason	<input type="checkbox"/>
I understand that the information collected will remain anonymous prior to be shared with other European centres that will only have access to non identifiable information	<input type="checkbox"/>

I understand that in the future I may be contacted to be asked questions regarding my clinical status in relation to my AVR operation	<input type="checkbox"/>
I agree to take part in the E-CABG registry	<input type="checkbox"/>

I, the undersigned, have read, understood and agree to the above conditions

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

33. N.A.