TRanscatheter **A**ortic-Valve Implantation with or without on-site **C**ardiac **S**urgery: the TRACS trial

Version number 2 of February 20, 2024

Signature page, approval of Study Protocol

I, the undersigned, have read and understand the protocol and agree that it contains all necessary information for conducting the study for my position in the study and I agree to conduct the trial as set out in this study protocol, the current version of the World Medical Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Study Principal Investigator

_____ _____

Date: Gianmarco Iannopollo, MD

Study Chair

_____ _____

Date: Gianni Casella, MD

Study Chair

_____ _____

Date: Vincenzo Guiducci, MD

Investigator Statement

I, the undersigned, have read and understand the protocol and agree that it contains all necessary information for conducting the study for my position in the study and I agree to conduct the trial as set out in this study protocol, the current version of the World Medical Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site: _____

Address: _____

Principal Investigator: _____

_____ _____

Date: Signature

Table of contents

1 STUDY SYNOPSIS

Study Title	Transcatheter Aortic Valve Implantation with or without on-site Cardiac Surgery: the TRACS trial
Protocol version	V2
Date	February 20, 2024
Study Sponsors	Azienda USL di Bologna, Bologna, Italy Azienda Ospedaliero Universitaria di Ferrara, Cona (FE), Italy Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy ***The present trial received the endorsement of the Italian Health Minister that partially supported the conduction of the study with the grant GR-2021-12374295 (Ricerca Finalizzata 2021)***
Study Principal Investigator	Gianmarco Iannopollo, MD
Study Chairs	Gianni Casella, MD Vincenzo Guiducci, MD
Study Objectives	The primary efficacy objective is to determine whether a TAVI pathway based on experienced operators who perform the procedure in the center without on-site cardiac surgery is non inferior compared to the one with the same team who perform the procedure in the center with on-site cardiac surgery in terms of all-cause death, stroke and rehospitalization for cardiovascular cause.. The primary safety objective is to demonstrate that mortality associated with periprocedural complications actionable by emergent cardiac surgery did not differ between study arms.
Study design	TRACS is an all-comer, prospective, randomized, multicenter, open-label trial with blinded adjudicated evaluation of outcomes (PROBE). The TRACS trial will involve centers without on-site cardiac surgery, but with experienced operators already performing TAVI at the referring center with on-site cardiac surgery. Thus, participating centers and their study TAVI operators must follow selective criteria for eligibility. Participants will be recruited after Heart Team indication to TAVI procedure. The eligibility of each single patient to the study MUST BE CONFIRMED and VALIDATED by unanimous decision of the Heart Team. Study patients will be randomized in a 2:1 fashion to TAVI procedure performed by the same experienced operators either in the center without on-site cardiac surgery or in the referring center with on-site cardiac surgery.
Study arms	EXPERIMENTAL ARM: TAVI WITHOUT ON-SITE SURGERY After randomization, study TAVI operators of the participating center will schedule

	the patient for TAVI in their hospital without on-site surgery. CONTROL ARM: TAVI WITH ON-SITE SURGERY After randomization, the patient will immediately be placed on the waiting list of the referring center with on-site cardiac surgery. Study TAVI operators of the participating center will perform the TAVI procedure in the hospital with on-site surgery according to the waiting list schedule of the latter.
Number of participants	566
Trial Location	Approximately 20 Italian centers without on-site cardiac surgery
Requirements for participating centers	1. Availability of standard operating procedure with a cardiac surgery department for an established, weekly Heart Team discussion 2. Availability of standard operating procedure for the rapid transfer of patients with procedural complications to cardiac surgery with a maximum delay of 60 minutes (maximum distance between centers 90 km) 3. Five-year experience in screening, selection, and management of TAVI patients 4. At least 2 certified operators or a dedicated intercenter team performing the TAVI procedure (see detailed criteria list) 5. At least 3-year experience in performing TAVI procedures in a center with on-site cardiac surgery, with participation (as equipe) in at least 100 TAVI procedures 6. At least 5-year experience in advanced cardiac imaging including transoesophageal echocardiography and cardiac computed tomography 7. On-site vascular surgery or on-site availability of certified surgeon and operating room allowing the surgical treatment of vascular complications 8. On-site electrophysiology laboratory (permanent pacemaker implantation)
Requirements for study TAVI operators	1. At least 5-year experience in coronary interventions 2. More than 75 PCIs per year 3. Experience in the use of tools for retrieval of intravascular foreign bodies 4. Experience in pericardiocentesis 5. Experience with ultrasound-guided puncture of the femoral artery 6. Experience in suture-mediated closure of femoral artery access 7. Experience in the management of peripheral vascular complications 8. At least 2-years experience in TAVI procedures as first and second operator 9. At least 50 TAVI procedures as first operator 10. More than 20 TAVI by year
Inclusion criteria	1. Severe aortic stenosis 2. Indication to TAVI confirmed by the Study Heart Team AND one of the following: 1. Inoperable due to prohibitive operative risk 2. High surgical risk as defined as STS score >8%

	3. The presence of at least one clinical factor that, by unanimous judgment of the Study Heart Team, compromises the benefit/risk ratio in the case of emergent cardiac surgery: • Porcelain aorta or severely atherosclerotic aorta • Frailty/Reduced physical performance • Cognitive impairment, dementia, or Parkinson's disease • Severe liver disease/cirrhosis • Hostile chest • Internal mammalian artery or other critical conduit(s) crossing midline and/or adhering to the posterior table of the sternum • Severe pulmonary hypertension and/or severe right ventricular dysfunction • Severe Chronic Obstructive Pulmonary Disease (COPD) • Age ≥85 years **It is mandatory for the inclusion in the study that the Study Heart Team confirm by unanimous judgment the eligibility of each single patient. It is in charge of the Study Heart Team to weight the feasibility and to estimate the eventual efficacy of emergent cardiac surgery and based on this assessment to proceed or not with the eligibility. If the Study Heart estimates the emergent cardiac surgery feasible and potentially effective, the patient cannot be considered eligible.**
Exclusion criteria	1. Unsuitable for transfemoral TAVI 2. Emergent TAVI 3. Noncardiovascular comorbidity reducing life expectancy to <1 year 4. Any factor precluding 1-year follow-up 5. Refusal informed consent
Primary endpoint	One-year cumulative occurrence of all-cause death, stroke and hospital readmission for cardiovascular causes *The adverse events will be collected from the time of randomization, also considering adverse events during the waiting time for the TAVI procedure.*
Secondary efficacy endpoints	• All-cause death • Cardiovascular death • Myocardial infarction • Hospital admission for cardiovascular cause • Hospital admission for heart failure • Cerebrovascular accident • Ischemic stroke

	• Hospital admission for pneumonia (± respiratory failure) • Need for balloon aortic valvuloplasty for emergent condition • Quality of life measured with the Eq-5D and KCCQ-12 scales • Time spent on the waiting list before TAVI
Primary safety endpoint	Death due to periprocedural complications that can be addressed with emergent cardiac surgery
Other safety endpoints	• Cardiac tamponade • Bleeding • Kidney failure (requirement of renal replacement therapy) • Severe aortic regurgitation (aortic regurgitation according to current guidelines) • Multiorgan failure (failure of at least two organ systems) • Vascular access site and access related complications • Conduction disturbances and arrhythmias • Endocarditis • Valve thrombosis • Valve malpositioning • Valve embolization • Ectopic valve deployment • TAV-in-TAV deployment
Assessment Schedule	Pre-eligibility screening, inclusion, randomization, TAVI, 1-month visit after TAVI, 6-month visit after TAVI, 12-month visit after TAVI, and every 12 months thereafter.
Study Duration	Enrollment will occur over approximately 2 years with an expected minimum follow-up of 12 months. All patients will be followed until 3 years.
Clinical Event Adjudication Committee	A blinded Clinical Event Adjudication Committee will adjudicate adverse events.
Data and Safety Monitoring Board	An independent Data and Safety Monitoring Board will advise the Steering Committee on the safety aspects and overall progress of the study.
Statistical Considerations	The estimated rate of the primary endpoint is around 30%, considering the characteristics of the study population and the inclusion of adverse events before TAVI [1-29]. Overall, 560 (187 control arm and 373 experimental arm) patients are required to exclude a difference in favor of the control group of more than 10% (alpha=5% and ß=20%). Considering a 1% attrition rate final sample size is inflated to 566 patients.

2 BACKGROUND

2.1 Indication to the TAVI procedure and the role of the Heart Team

Transcatheter aortic valve implantation (TAVI) has become standard therapy for elderly patients with symptomatic aortic stenosis. The PARTNER trials, CoreValve US High Risk, SURTAVI and Evolut Low risk studies were pivotal in presenting robust evidence for the safety, feasibility, and efficacy of TAVI with both self- and balloon-expandable prostheses in the management of aortic stenosis in patients from high to low surgical risk and paved the way for clinical use worldwide [1-7]. Accordingly, valvular heart disease (VHD) guidelines suggested TAVI as a valid option for all patients aged 75 years or more, when decisions concerning treatment and intervention derive from an active and collaborative Heart Team with expertise in VHD. The Heart Team is a group of qualified healthcare professionals comprising clinical and interventional cardiologists, cardiac surgeons, interventional imaging specialists, cardiovascular anesthesiologists, and other specialists if necessary (e.g., heart failure specialists or electrophysiologists, geriatrics). The role of the Heart Team is crucial, since it can comprehensively discuss the accuracy of surgical risk scores, consider the additional role of unaccounted comorbidities or frailty, and perform a risk-benefit analysis that includes other factors not necessarily caught in standard procedures or protocols. Therefore, Heart Teams play a crucial role in decision making and the European Society of Cardiology strongly supports its consultation for the treatment of VHD [8].

2.2 Heart Valve Centers and TAVI in centers with on-site cardiac surgery

The VHD guidelines support Heart Valve Centers as centers of excellence in the treatment of VHD to provide optimal quality of care with a patient-centered approach. This is achieved through high procedural volume in conjunction with specialized training, continuous education, and focused clinical interest. The main requirements of a Heart Valve Centre are on-site institutional cardiology and cardiac surgery (CS) departments, an active and collaborative Heart Team, and the institution of a Heart Valve Clinic (Table 1). The latter consists of a structured and dedicated outpatient clinic where the cardiologist in charge should have compentecies in treating patients with VHD. Recent evidence shows that access to these Heart Valve clinics improves outcomes in patients with aortic valve stenosis. Beside the whole spectrum of valvular interventions, expertise in interventional and surgical management of coronary artery disease (CAD), vascular diseases, and complications must be available [8].

Requirements
Centre performing heart valve procedures with institutional cardiology and cardiac surgery departments with 24 h/7-day services. **Heart Team:** clinical cardiologist, interventional cardiologist, cardiac surgeon, imaging specialist with expertise in interventional imaging, cardiovascular anaesthesiologist. **Additional specialists if required:** heart failure specialist, electrophysiologist, geriatrician and other specialists (intensive care, vascular surgery, infectious disease, neurology). Dedicated nursing personnel is an important asset to the Heart Team. The Heart Team must meet on a frequent basis and work with standard operating procedures and clinical governance arrangements defined locally. A hybrid catheterization laboratory is desirable. The entire spectrum of surgical and transcatheter valve procedures should be available. High volume for hospital and individual operators.
Multimodality imaging including echocardiography, CCT, CMR, and nuclear medicine, as well as expertise on guidance of surgical and interventional procedures.
Heart Valve Clinic for outpatient and follow-up management.
Data review: continuous evaluation of outcomes with quality review and/or local/external audit. Education programmes targeting patient primary care, operator, diagnostic and interventional imager training and referring cardiologist.

CCT = cardiac computed tomography; CMR = cardiac magnetic resonance.

Table 1: Requirements for a Heart Valve Center according to the ESC 2021 VHD Guidelines.

2.3 The burden of complications during TAVI

Despite the optimization of the technique, several complications may occur during the TAVI procedure. The major determinants of complications are the following:

- Expertise of the operators;
- Comorbidities (age) of the patients

At the beginning of the TAVI experience, there was a strong discrepancy in the classification and reporting of complications and adverse events. Trying to standardize definitions and reporting of the complications across centers, trials and registries, the Valve Academic Research Consortium (VARC) consensus manuscripts were published. The first consensus (VARC-1) was published in January 2011 with the goal of achieving consensus for (i) selecting appropriate clinical endpoints reflecting device, procedure and patient-related effectiveness and safety, and (ii) standardizing definitions for single and composite clinical endpoints, for transcatheter aortic valve implantation (TAVI) clinical trials [9]. This first document was updated on 2012 (VARC-2) and 2021 (VARC-3) to revisit the selection and definitions of TAVI-related clinical endpoints and make them more suitable to the needs of clinical trials. The Table below shows the occurrence of complications in the first 30 days after TAVI according to VARC-2 classification [10].

Table 3. Results of individual study based on VARC-2 Recommendations.

Study	All-cause mortality (30 days)	Cardiovascular mortality (30 days)	Mortality (1 year)	Myocardial infarction, n (%)	Stroke, n (%)	Bleeding, n (%)	Acute kidney injury, n (%)	Vascular access site and access-related complications, n (%)	Need for new PPM, n (%)
Balloon-expandable Sapien Prosthesis Registry									
The ITER Registry [20]	137 (7.2)	-	286 (15.0)	**29 (1.5)***	54 (2.8)	499 (26.2)	**155 (8.6)***	314 (16.5)	116 (6.1)
The PARTNER II SAPIEN 3 Registry [18]									
- HR/inoperable	13 (2.2)	8 (1.4)	-	3 (0.5)	12 (2.1)	**117 (24.2)***	50 (7.6)	75 (12.9)	77 (13.3)
- IR	12 (1.1)	10 (0.9)	-	3 (0.3)	34 (3.2)	**164 (15.2)***	56 (5.2)	131 (12.2)	109 (10.1)
A Spanish single center TAVI Registry [19]	(12.7)	(6.35)	(25.4)	2 (2.6)	2 (2.6)	9 (11.4)	14 (17.8)	12 (15.2)	3 (3.8)
The Swiss TAVI Registry [17]									
-Sapien 3	5 (3.3)	4 (2.6)	-	2 (1.3)	2 (1.3)	14 (9.2)	7 (4.6)	8 (5.2)	26 (17.0)
-Sapien XT	20 (4.5)	19 (4.3)	-	0 (0.0)	18 (4.0)	66 (14.8)	26 (5.8)	75 (16.9)	49 (11.0)
Rouen TAVI Registry [16]	11 (4.7)	-	(23.2)	-	-	**18 (7.6)***	55 (23.3)	-33 (14.0)	-
The SOURCE ANZ Registry [21]	10 (7.8)	-	23 (17.8)	5 (3.9)	5 (3.9)	-	20 (15.6)	13 (10.1)	6 (4.7)
Self-expandable CoreValve Prosthesis Registry									
The Italian CoreValve Registry [22]	80 (6.1)	62 (4.7)	-	13 (0.9)	27 (2.0)	348 (26.4)	**234 (17.8)***	**93 (7.1)***	311 (23.6)
Mixed Registry									
WIN-TAVI Real-World Registry [23]	40 (3.4)	38 (3.3)	-	2 (0.2)	13 (1.3)	**45 (4.4)***	**13 (1.3)***	**80 (7.7)***	118 (11.6)
The Pooled-Rotterdam-Milano-Toulouse Registry [30]	10 (6.0)	8 (4.8)	-	-	6 (3.6)	**4 (2.4)***	12 (7.2)	**8 (4.8)***	27 (16.2)
The Asian TAVR Registry [31]	21 (2.5)	14 (1.7)	81 (10.8)	-	32 (3.8)	92 (10.8)	**28 (3.3)***	82 (9.7)	80 (9.5)
Inohara et al. 2016 (26)									
The Japan OCEAN TAVI Registry	0 (0)	0 (0)	-	**2 (1.5)***	2 (1.5)	23(17.2)	**2 (1.5)***	17(12.7)	8 (6.0)
Nassy database	1 (0.6)	1 (0.6)	-	**0 (0)***	1 (0.6)	30(16.8)	**2 (1.1)***	27(15.2)	39 (21.9)
TAVI-Karlsruhe Registry [28]									
-TA	(6.1)	(4.1)	-	**(2.7*)**	(1.7)	(28.8)	(35.1)	(2.9)	(10.7)
-TF	(6.5)	(5.1)	-	**(1.7*)**	(2.3)	(28.6)	(19.9)	(19)	(15.7)
The Brazilian Registry [24]	(9.1)	(7.9)	(21.5)	(0.7)	(3.5)	(18.5)	(20.0)	(13.8)	(24.4)
PRAGMATIC Multicenter Study [15]	63 (5.9)	56 (5.3)	187 (18.5)	**12 (1.1)***	42 (4)	460 (43.3)	257 (24.2)	227 (21.4)	165 (15.6)

Study	All-cause mortality (30 days)	Cardiovascular mortality (30 days)	Mortality (1 year)	Myocardial infarction, n (%)	Stroke, n (%)	Bleeding, n (%)	Acute kidney injury, n (%)	Vascular access site and access-related complications, n (%)	Need for new PPM, n (%)
Multicenter registry from America and Europe [27]	65 (5.7)	-	-	-	40 (3.5)	**57 (5.0)***	-	**136 (12.0)***	173 (15.3)
The Royal Prince Alfred Hospital TAVI Program [26]	3 (3.0)	2 (2.0)	7 (7.0)	**2 (2.0)***	4 (4.0)	30 (30.0)	16 (16.0)	17 (17.0)	13 (13.0)
The University Hospital Zurich TAVI Registry [29]	32 (9.1)	31 (8.7)	(21.0)	(2.0)	(2.9)	(4.6)	(5.7)	(7.4)	(18.9)
Other TAVI System									
Nordic Lotus-TAVR registry [32]	3 (1.9)	-	-	-	5 (3.2)	**3 (1.9)***	**2 (1.3)***	**4 (2.6)***	43 (27.9%)
DISCOVER Study [33]	1 (1.0)	1 (1.0)	10 (10.0)	1 (1.0)	7 (7.0)	**9 (9.0)***	**1 (1.0)***	13 (13.0)	17 (17.0)

The data can be summarized as follows:

- 30-day all-cause mortality ranges from 0% to 9.1%
- 30-day cardiovascular mortality ranges from 0% to 8.7%
- 1-year mortality ranges 15% from 25.4%
- Myocardial infarction ranges from 0% to 3.9%
- Stroke ranges from 0.6% to 7%
- Bleeding ranges from 1.9% to 43.3%
- Vascular access site and access-related complications range from 2.6% to 21.4%
- The need for a new periprocedural pacemaker ranges from 3.8% to 27.9%

As expected, the occurrence of complications after TAVI widely ranges between studies. Anyway, it is clear that most complications are due to access-related complications, bleeding and the need for pacemaker, while emergent surgical turn-down is rare (see below). Furthermore, the rate of these complications is declining due to procedural (echo-guidance for the femoral artery puncture, etc.) or technical valve improvements (less need of pacemaker, reduced sheath size, etc.). Thus, several of these complications could be anticipated. However, if they occur, their treatment rarely requires the involvement and availability of on-site cardiac surgery. In summary, to minimize the incidence and the consequence of complications, the key points are:

- Meticulous procedural planning
- Experience of the operator in the access site management
- Vascular surgery department or on-site surgeon and operating room able to treat vascular complications
- Electrophysiology laboratory

2.4 Emergent cardiac surgery during TAVI

The causes, rates, and outcomes of patients undergoing emergent cardiac surgery (ECS) during TAVI interventions have been of great interest. A meta-analysis of more than 9000 patients from 46 different studies was published in 2013. These patients were treated with first-generation TAVI devices, large bore delivery systems, and without using gated cardiac CT for valve sizing and procedural planning. Rates of ECS were 1.1% for the overall population and 0.6% for patients treated through the transfemoral route. The most frequent indication for surgery was valve embolization/migration in 41% of cases. **Mortality rates for patients undergoing ECS were 67% at 30 days** [11]. With the advent of gated cardiac CT and the re-positionable self-expanding THV, the risk of valve embolization has significantly decreased. The short-term outcomes were assessed in the prospective German TAVI registry published in 2013. Bailout surgery was required in 24 (1.2%) of 1975 enrolled patients. The most common causes of conversion to emergent surgery were annular rupture and dissection or perforation of the aorta. **Mortality rates of patients**

undergoing ECS were still high (45.8% at 30-days follow-up) [12]. An interim analysis from the all-comer – prospectively collected German Aortic Valve Registry (GARY) analyzed intra- and post-procedural complication rates during TAVI in patients treated from 2011 to 2013. The analysis included 15,964 patients, 70.7% of whom were performed by transfemoral approach. **Urgent sternotomy was required in 201 (1.3%) patients, 61 (30.3%) of these patients underwent TAVI using a transapical approach**. **In-hospital mortality was 42.3% for patients requiring ECS in comparison to 5.2% in the overall population ($p < 0.05$)**. Over time, there was a numerical, not statistically significant, decline in the need for urgent sternotomy from 1.6% in 2011 to 1.1% in 2013 ($p = 0.13$). Univariate and multivariate analysis failed to identify any predictor of the occurrence of emergent cardiac surgery during TAVI, although patients who required cardiac surgery were more likely to undergo emergent TAVI, had higher rates of general anesthesia, longer procedural time, and a greater degree of aortic insufficiency after valve implantation. This study might not reflect current practice, since the transapical approach is seldom used nowadays [13]. A more contemporary study analyzed predictors and outcomes of ECS in 1775 TAVI patients treated from 2011 to 2016 in a single-center high-volume hospital. Over five years, 32 (2.1%) of patients required conversion to open cardiac surgery. **The conversion rates to open surgery decreased over time, from 6% in 2011 to 1% in 2016**. The most common cause of ECS was pericardial tamponade in 47% of cases, followed by valve embolization (28%) and annular rupture (16%). **Mortality at 30-day and 1-year in patients requiring urgent cardiac surgery was high 44% and 59.3%**. The authors found no baseline or procedural related predictors for ECS in their analysis. Of note, rates of conversion to open surgery according to access approach transfemoral vs transapical were not specified [14]. Eggebrecht et al. published an independent, international, and multicenter trial of 27,760 transfemoral TAVI from 79 centers, analyzing outcomes of patients requiring ECS during TAVI. Procedures were performed over the years 2013 to 2016, and the need for ECS widely varied across centers ranging from 0% to 6.7%. **In 25 centers, performing TAVI in 3821 (13.3%) patients, not even a single case required salvage surgery during TAVI interventions**. Overall, the rates for emergent cardiac surgery were 0.76% and significantly decreased from 1.07% in 2013 to 0.68% and 0.73% in 2015 and 2016, respectively. The most frequent causes for ECS were left ventricular perforation, annular rupture, and valve embolization/migration in 28%, 21%, and 13% of patients, respectively. **Immediate post-procedural mortality was 34% and at one-year follow-up only 22% of patients were alive**. Older age (>85-year-old) and annular rupture were independent predictors of mortality in multivariate analysis. **The rates of emergent surgery were similar whether patients were treated in high-volume versus low-volume centers**. *The authors concluded that although rare, ECS for the salvage of complicated transfemoral TAVI carries a grim prognosis with survival rates at 1-year follow-up below 25%. Thus, the Authors recommend that prevention of complications should be the main strategy to improve outcomes in patients undergoing transfemoral TAVI* [15]. To date, the largest study reporting ECS during TAVI analyzed data of all 47,546 patients who underwent TAVI between the years 2011–2015 in the

USA. In this registry, the reported ECS rate was 1.17% (558 cases). The most frequent causes for ECS were valve dislodgement (22%), ventricular rupture (19.9%), and aortic valve annular rupture (14.2%). It should be noted that over the four years, the incidence of surgical bailout significantly decreased, and reached 1.04% in the third tertile. **ECS was associated with significantly worse short and long-term outcomes (in-hospital and one-year mortality of 49.6% vs 3.5% and 59.8% vs 17.1%, respectively)**. The independent predictors of ECS were female sex, low hemoglobin, reduced left ventricular ejection fraction, non-elective cases, balloon-expandable valve, and non-femoral access. In addition, the progressive reduction of the need of ECS during TAVI has switched the surgical back-up to a virtual one, being TAVI performed in conventional cath-lab while surgical rooms are running as usual [16].

In conclusion, ECS during TAVI is rare (<1%). Adequate patient selection and meticulous procedural planning are the most effective strategies to minimize complications during TAVI. Patients undergoing ECS are older, have comorbidities and their prognosis tends to be poor despite ECS. Indeed, 1-year survival after ECS is around 20%-30%.

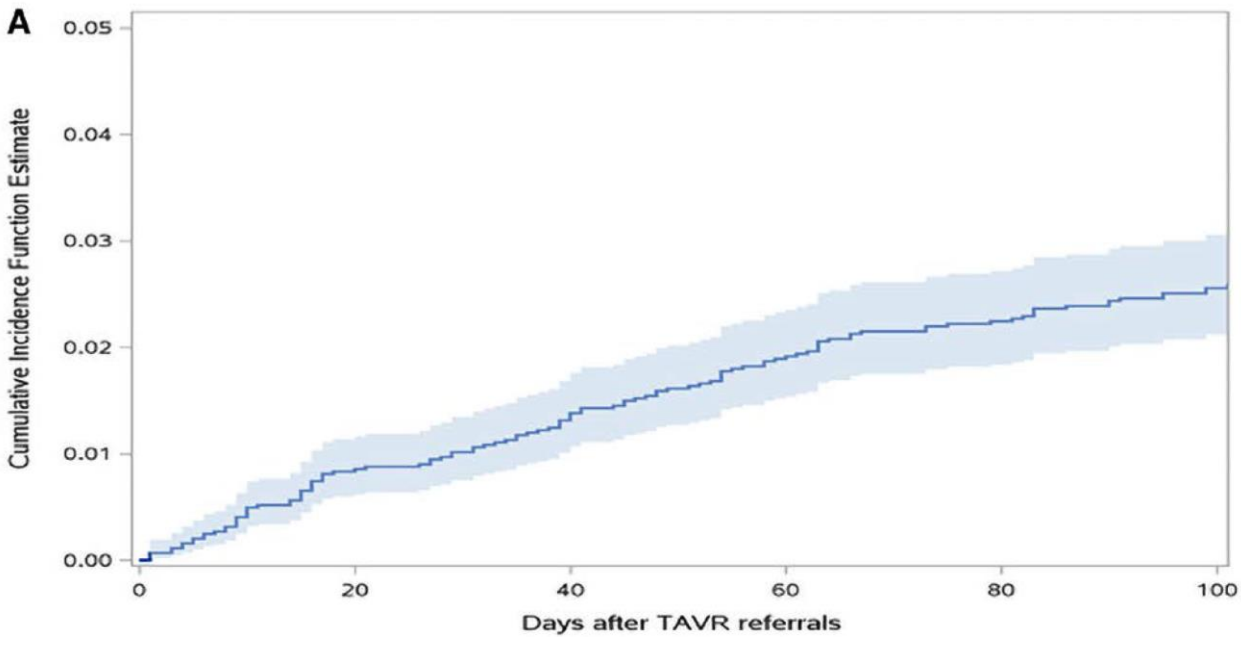
Table 2
Summary of TAVI results from recent years.

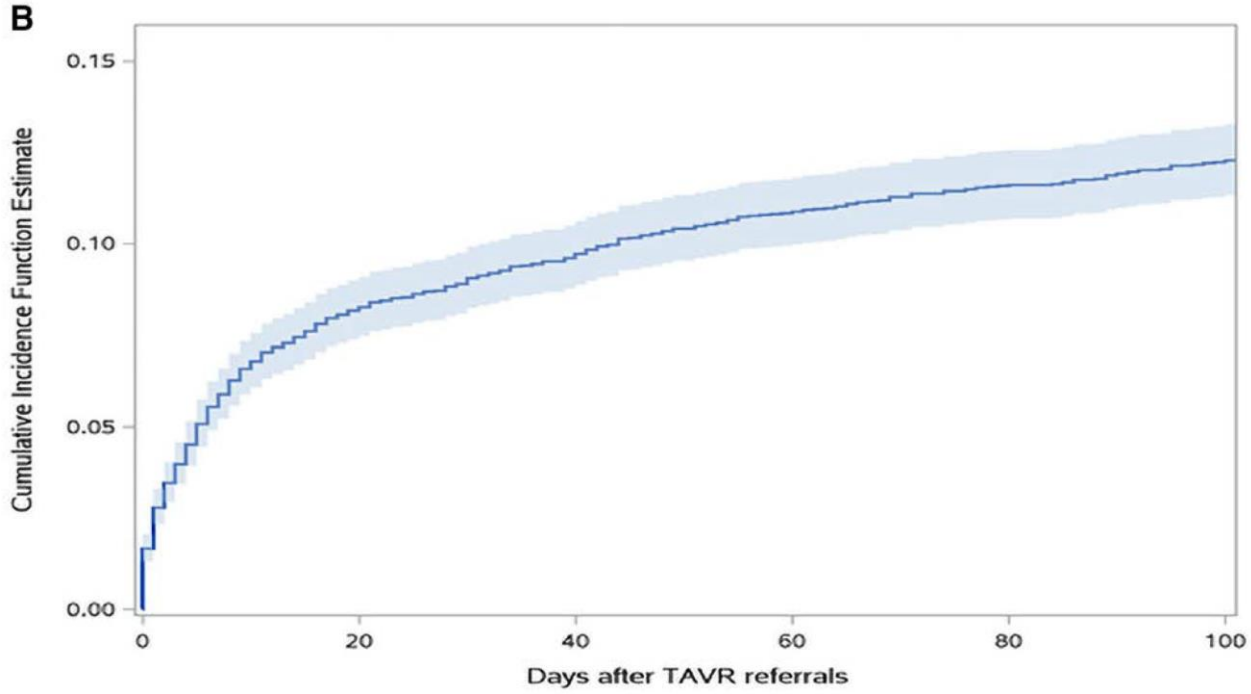
Ref and publication year	Name	Number of patients	Emergent cardiac surgery	Vascular complications
[26] 2013	Meta-analysis	9000 [46 studies]	0.6%	
[27] 2013	Prospective German TAVI registry	1975	1.2%	4.7%
[28] 2014	SOURCE registry	2307	1.2%	4.0%
[29] 2015	GARY registry	15,964	1.1%	4.1%
[30] 2018	Single center	1775	1%	NA
[31] 2018	Multicenter transfemoral TAVI registry from 79 centers	27760	0.76%	NA
[32] 2019	USA between 2011 and 15	47,546	1.17%	7.1%
[33] 2020	FRANCE-TAVI 2013–15			6.4%–7.3%
[34] 2021	CHOICE-CLOSURE trial	516		7.4–11.1%

2.5 The burden of the waiting time for TAVI

Randomized clinical trials (RCT) showed technical feasibility and clinical effectiveness of TAVI in low to high surgical risk patients as well as inoperable ones [4, 7]. Therefore, after careful screening by the Heart Team, according to current guidelines, TAVI has a Class IA recommendation for all patients aged 75 years or older, independently of their surgical risk [8]. Consequently, the number of patients who are referred to hub centers with on-site CS for TAVI is largely growing and this could overtake their capabilities. Thus, waiting list for TAVI is dangerously lengthening and could expose patients at the risk of events while on this wait. Long wait times have negative consequences, including patient mortality, morbidity, repeated hospitalizations, and functional deterioration. Several studies demonstrated that prolonged TAVI wait times are associated with adverse outcomes. In a study from Spain, the mean waiting time for TAVI was 2.9 ± 1.6 months, and the mortality rate was 2.7% [8/300 patients]. **Of the patients who died while on the waiting list, half did so in the first 100 days** [17]. From May 2008 to May 2011, 170 high-risk patients with symptomatic severe AS were referred to an experienced TAVI center in Edmonton Alberta, Canada.

Seventeen patients (10%) died while waiting for a complete assessment [18]. A group from Almada, Portugal, reported in the 2020 ESC annual meeting on 120 consecutive AS patients (54% male, mean age 75 ± 9 years) referred between 2014 and 2018 to a single center. During the waiting period, there were 13 (11%) patients who were hospitalized due to heart failure and 7 (6%) patients who died. The median time between referral and the occurrence of the primary endpoint was 3 months [42]. In Israel,, data on mortality of patients with patients with AS diagnosed in 9 non-TAVI centers and referred to a TAVI center found that during a six-month period in 2019 there were 203 patients patients referred with a mortality rate of 4.9% (10/203) during the waiting period [19]. **Data from Ontario (Canada) showed that during the initial period of development of TAVI therapy, patients with TAVI showed mortality rates of 10% to 14% while in the waiting period** [20]. **In Ontario from 2010 to 2016, the cumulative probability of TAVI wait list mortality was 4.3% in a predominantly inoperable and high-risk population** [21]. From recent reports, the cumulative probability of wait-list mortality and heart failure hospitalization at 80 days in Canada was 2% and 12%, respectively, with a relatively constant increase in events with increased waiting times. From a cohort consisting of 22,876 referrals for aortic valve replacement, with (n = 8098) TAVI and (n = 14,778) SAVR referrals, the mean and median waiting times for the overall AVR cohort were 87 and 59 days, respectively. The TAVI sub cohort had longer waiting times (median 84 days) compared with the SAVR sub cohort (median 50 days). **Year over year, there was a statistically significant increase in wait-times ($p < 0.001$) for TAVI. The waiting time mortality was 5.2% for TAVI, while the cumulative probability of hospitalization for heart failure was 7.7%** [21]. Current waiting time for TAVI in Italy ranges from 2 to 6 months, with a strong variability based on regional healthcare system organization. In the Emilia-Romagna region, the median wait time is m 6 months in 52% of patients scheduled for TAVI (Direzione Generale Cura della Persona, Salute e Welfare, Regione Emilia-Romagna).





2.6 The balance between the burden of the waiting list and saved lives from ECS

As stated above, TAVI procedure may cause lethal complications that ECS may save in half of the cases. However, it should be considered that the same patients carry a significant risk of events while waiting for TAVI in the center with on-site CS if such wait is longer than 2-3 months. To date, no study has investigated the balance between the two burdens, but available data could support an estimate.

If we supposed to have 1000 patients with indication to TAVI, 10 of them are expected to need ECS during TAVI procedure. Based on the literature, ECS will save the life of 5 (50%) patients, mainly the youngest, with few comorbidities and less complex complications. On the contrary, we could expect that in a center without on-site CS all 10 patients would die. The absolute risk reduction (AAR) in the center with on-site CS is 0,005 with a **number needed to treat (NNT) equal to 200 patients**.

On the other hand, according to the literature, in patients waiting at least 3 months for TAVI in a center with on-site CS, we could expect a mortality of around 4% during this wait. If extending TAVI of inoperable or high surgical risk to centers without on-site CS reduces the time spent on the waiting list by the 50%, we could expect that even mortality could be reduced to 2%. The absolute risk reduction of halving the waiting time for TAVI could be 0,02 with a **number needed to treat equal to 50 patients**.

Although this hypothesis should be taken with caution, the different weight of these NNTs should be considered.

2.7 Preliminary experience of the TAVI procedure in centers without on-site cardiac surgery

Preliminary data from Austrian, German and Spanish registries show that although patients undergoing TAVI in hospitals without a CS department on site have a higher risk profile, after adjustment for potential confounders, compared to those treated in centers with on-site cardiac surgery, short and long-term mortality are similar [22-26].

Table 1
Summary of studies reporting TAVI in centers without on-site cardiac surgery.
[In the reports from Austria and Germany (refs 21–24), during the procedure a visiting cardiothoracic surgical team was present in the center without on-site surgery for backup].

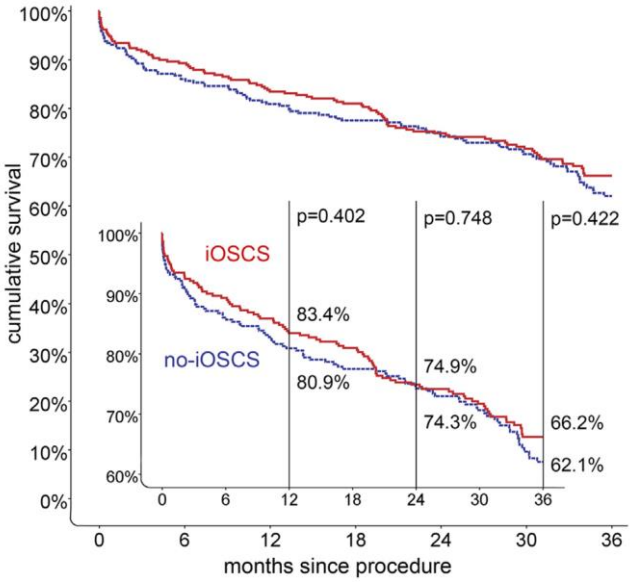
	Publication year	Study period		No on site		
Eggebrecht [21]	2014	2009–10	Germany	178	1254	Mortality at 30 days: 6.2% vs. 8.3%, p = NS
Gafoor [22]	2015	2005–12	CardioVascular Center, Frankfurt, Germany (Single Center)	97	–	16.5% vascular complication rate 30-day mortality 3.1%, stroke 5.2% major bleeding 8.2%
(AQUA) registry [23]	2016	2013–14	Germany	1332	16,587	In-hospital mortality (3.8% vs 4.2%, p = 0.396) sternotomy (0.3% vs 0.7%, p = 0.088)
Egger [24]	2018	2011–16	Austria	290	1532	After propensity matching; in hospital, one month, one year, and 3 years all-cause mortality rates were not significantly different
Roa Garrido [25]	2019	2015–17	Spain	384		Technical success 96.6% in-hospital mortality 2.1%, one year mortality 12.2%

Furthermore, in Italy, the Cardiology Department of Bolzano, a center without permanent on-site CS but with temporary surgical backup during TAVI, has performed 100 TAVI procedures with good procedural outcomes. Similar experiences exist all around the world.

The first study to assess outcomes of patients with severe symptomatic AS treated with TAVI at institutions without on-site cardiac surgery was published in 2014. Eggebrecht et al., compared 1254 patients treated at 27 German hospitals with on-site cardiac surgery to 178 patients (8 institutions) without on-site cardiac surgery. Patients underwent TAVI between 2009 and 2010 with first-generation self-expandable or balloon-expandable valves. The authors found no significant differences in rates of major post-procedural complications. ECS was needed in 4 patients (2.2%) treated in facilities without on-site cardiac surgery. Mortality at 30 days was not different between groups (8.3% vs 6.2%, p=NS for treatment in hospitals with vs. without on-site cardiac surgery, respectively). In-hospital mortality for patients who underwent ECS was greater than 40% in both groups [22]. Gafoor et al., reported outcomes of 97 patients with severe symptomatic AS and high-risk features treated with TAVI at a single center - the CardioVascular Center, Frankfurt, Germany with a visiting surgical team. Patients were treated with first-generation self-expandable Corevalve and balloon-expandable Edwards-Sapien devices (93.8% and 6.2% of patients, respectively). In this single-center experience, the procedural technical success was 100%. There were no conversions to surgery. Two patients with cardiac tamponade were successfully treated with percutaneous pericardiocentesis. The authors concluded that TAVI of carefully selected patients can be safely and effectively performed in hospitals with a visiting surgical team [23].

The AQUA (Applied Quality Improvement and Research in Health Care) registry is a mandatory data collection for all inpatient procedures in Germany. In 2016, a comparative analysis of 17,919 TAVI patients

enrolled in the AQUA registry analyzed outcomes of patients undergoing trans-femoral TAVI in hospitals with (n=16,587) vs. without (n=1332) on-site cardiac surgery departments. Heart teams in hospitals without on-site cardiac surgery departments were compounded by visiting collaborating surgical physicians. At baseline, patients treated in hospitals without on-site cardiac surgery departments were older and with higher predicted risks of operative mortality [logistic EuroSCORE I (23.2 ± 15.8 vs. 21.0 ± 15.4%, p-Value<0.001)]. This analysis found no difference in rates of in-hospital mortality (3.8% vs 4.2%, p=0.396) nor in rates of conversion to surgery (0.3% vs 0.7%, p = 0.088) between the groups. Moreover, patients treated in hospitals without on-site cardiac surgery departments showed less severe intra-procedural complications and were more frequently discharged home compared to their counterparts [24]. A matched analysis of the study population confirmed these results. Egger et al. published data from the Austrian TAVI registry. Only patients with prohibitive conditions for SAVR or at high surgical risk who underwent TAVI by transfemoral access were eligible for the analysis. In centers without on-site cardiac surgery departments, all procedures were performed in specially equipped catheter laboratories suitable for potential emergency thoracotomy. Cardiovascular anesthesiologists, cardiothoracic and vascular surgeons were present during each procedure to allow bailout surgery if indicated. Patients treated in institutions without on-site cardiac surgery departments (n =290) were compared to those treated in hospitals with on-site cardiac surgery departments (n = 1532). Patients in the former group were older and had higher rates of left ventricular dysfunction, coronary disease, and other comorbidities. This was reflected in a significantly higher logistic EuroSCORE 20.9% vs 14.2%, p<0.001, for patients treated in facilities without vs. with cardiac surgery departments on site. After propensity matching, in-hospital, one month, one year, and 3 years all-cause mortality rates were not significantly different between the groups [25].



An analysis based on data from Spain, examined the safety and feasibility of TAVI in centers without on-site cardiac surgery department, but with on-site vascular surgery and a cardiac surgery center of reference less

than 90 km away. The data included 384 patients from 10 Spanish centers. The median age of the patients in the cohort was 82.2, with a moderate average surgical risk of the population as calculated by the Logistic EuroSCORE (14.3 ± 5.3). All patients were not suitable for SAVR, according to heart team decision. The technical success rate was high [96.6%], with only one urgent surgical intervention required (ventricular perforation and cardiac tamponade). In-hospital cardiovascular mortality was 2.1%, and one-year mortality was 12.2% [26].

2.8 Key points of the background

- TAVI is a valid alternative to aortic valve replacement when indicated by Heart Team
- Current guidelines suggest performing TAVI in centers with on-site cardiac surgery
- TAVI is a safe and effective therapy when the procedure is performed by experienced operators
- The majority of complications during TAVI are access-site related complications, bleedings and the need of pacemaker. The management of these complications do not require on-site cardiac surgery
- Emergent cardiac surgery during TAVI procedure is rare (<1%)
- Despite emergent cardiac surgery, 30-day mortality is still high (more than 50%)
- The concentration of TAVI patients in few centers with on-site cardiac surgery is associated with a significant increase in the waiting time for the procedure
- The median waiting time for TAVI in Italy ranges from 2 to 6 months, with wide variability between centers and regions.
- Longer waiting time for TAVI are associated with mortality and hospital readmission for heart failure
- In inoperable or high surgical risk patients, reducing the waiting time for TAVI could have a potential positive impact superior to the potential harm of the lack of on-site cardiac surgery
- The best strategy to minimize complications during the TAVI procedure is the optimization of the indication of the Heart Team and the careful planning of the procedure by experienced operators

3 HYPOTHESIS

Based on this background, we hypothesize that in patients with severe symptomatic aortic stenosis (inoperable or at high surgical risk) TAVI procedure can be performed by experienced operators in centers without on-site cardiac surgery (CS) with a similar 1-year outcome compared to centers with on-site cardiac surgery. Indeed:

- Bleeding, access site-related complications, and pacemaker implantation are the most common complications of TAVI and their treatment does not require on-site cardiac surgery
- Complications needing emergent cardiac surgery are very rare (<1%) and, despite the surgical intervention, the mortality in this population remains very high (more than 50% at 30 days, near 80% at 1 year)
- A median waiting time for TAVI around 3 months before TAVI is associated with a risk of mortality and hospitalization for heart failure around 4% and 15%, respectively. There is a relatively constant increase in the probability of death or of hospitalization with increasing waiting times, with no threshold below which events rates flat.
- To allow the treatment of inoperable or high surgical risk patients in centers without on-site cardiac surgery, can significantly reduce the waiting time for TAVI (also in the center with on-site CS) and then the fatal adverse events that occur between the indication for TAVI and the TAVI itself.

Therefore, we assume that an indication shared by an experienced Heart Team and a procedure meticulously planned and performed by experienced operators are the most effective strategies to minimize periprocedural complications, independently of the presence or absence of on-site CS. This hypothesis is indirectly confirmed by preliminary analyses from centers performing TAVI without on-site CS. Therefore, the aim of the TRACS trial is to investigate if a TAVI pathway based on experienced operators who perform the procedure in the center without on-site cardiac surgery is non inferior compared to the one with the same team who perform the procedure in the center with on-site cardiac surgery in terms of outcomes..

4 STUDY ENDPOINTS

4.1 Primary efficacy endpoint

- 1-year cumulative occurrence of all-cause death, stroke and hospital readmission for CV cause

To test if a TAVI pathway based on experienced operators who perform the procedure in the center without on-site cardiac surgery is non inferior compared to the one with the same team who perform the procedure in the center with on-site cardiac surgery.

4.2 Secondary efficacy endpoints

- All-cause death
- Cardiovascular death
- Myocardial infarction
- Hospital admission for cardiovascular cause
- Hospital admission for heart failure
- Cerebrovascular accident
- Ischemic stroke
- Hospital admission for pneumonia (± respiratory failure)
- Need for balloon aortic valvuloplasty for emergent condition
- Quality of life measured with the Eq-5D and KCCQ-12 scales
- Time spent on the waiting list before TAVI

4.3 Primary safety endpoint

- Death due periprocedural complications actionable by emergent cardiac surgery

To test whether mortality due to periprocedural complications actionable by emergent cardiac surgery differs between the TAVI procedures performed in the center without on-site cardiac surgery and the TAVI procedures performed by the same team in the center with on-site cardiac surgery.

4.4 Other safety endpoints

- Cardiac tamponade
- Bleeding
- Kidney failure (requirement for renal replacement therapy)
- Severe aortic regurgitation (aortic regurgitation according to current guidelines)
- Multiorgan failure (failure of at least two organ systems)

- Vascular access site and access related complications
- Conduction disturbances and arrhythmias
- Endocarditis
- Valve thrombosis
- Valve malpositioning
- Valve embolization
- Ectopic valve deployment
- TAV-in-TAV deployment

5 STUDY DESIGN, SCREENING, INCLUSION AND RANDOMIZATION

5.1 Study design

The TRACS is an all-comer, prospective, randomized, multicenter, open-label trial with blinded adjudicated evaluation of outcomes (PROBE).

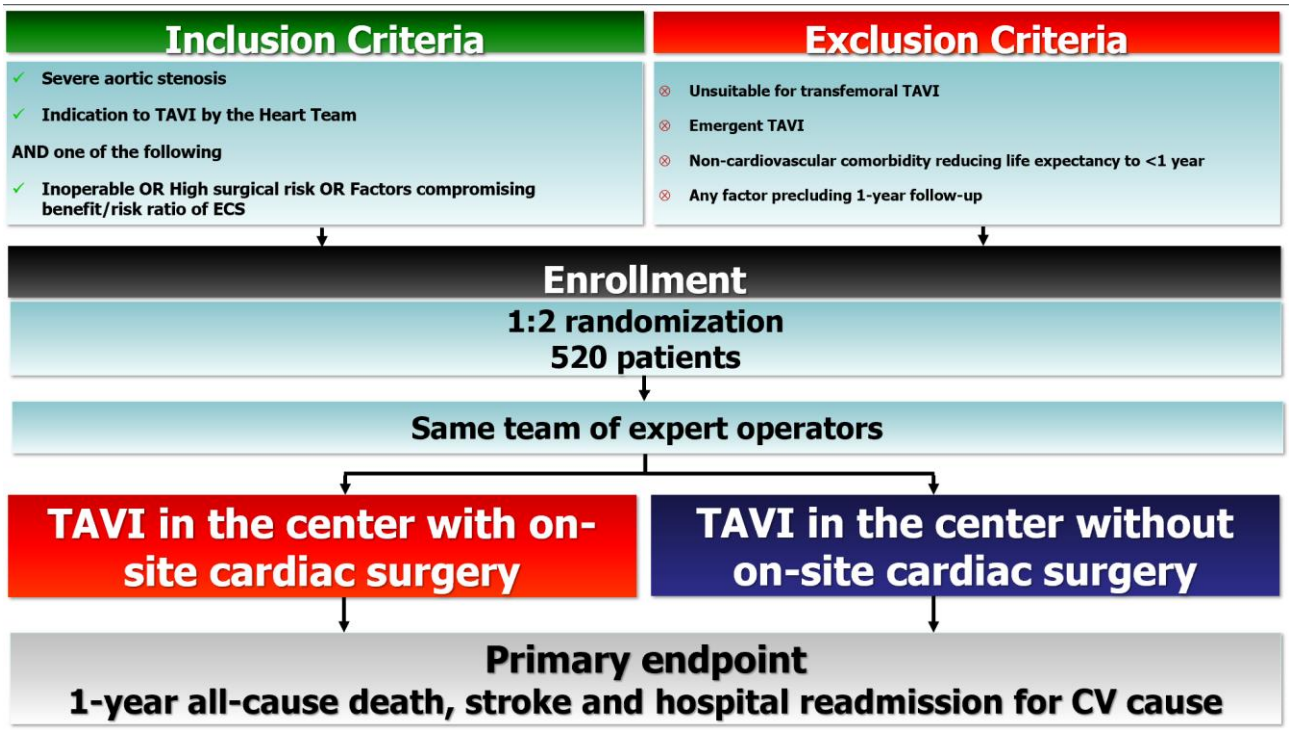
Participating centers of the TRACS trial are "**centers without on-site cardiac surgery**". A detailed list of the criteria required for being considered participating center is reported in the section number 9 (study definition). The final decision on inclusion or not of a participating center is on charge of the Data Safety Monitoring Board (DSMB).

Each participating center must identify:

- The "**study Heart Team"**
- The "**study TAVI operators**"

A detailed description of the study Heart Team composition and role and of the criteria required for being considered study TAVI operator is reported in the section number 9 (study definition). The final decision on the accreditation of the TAVI operator in the study is in charge of the Data Safety Monitoring Board.

The figure below summarizes the main characteristics of the study flow.

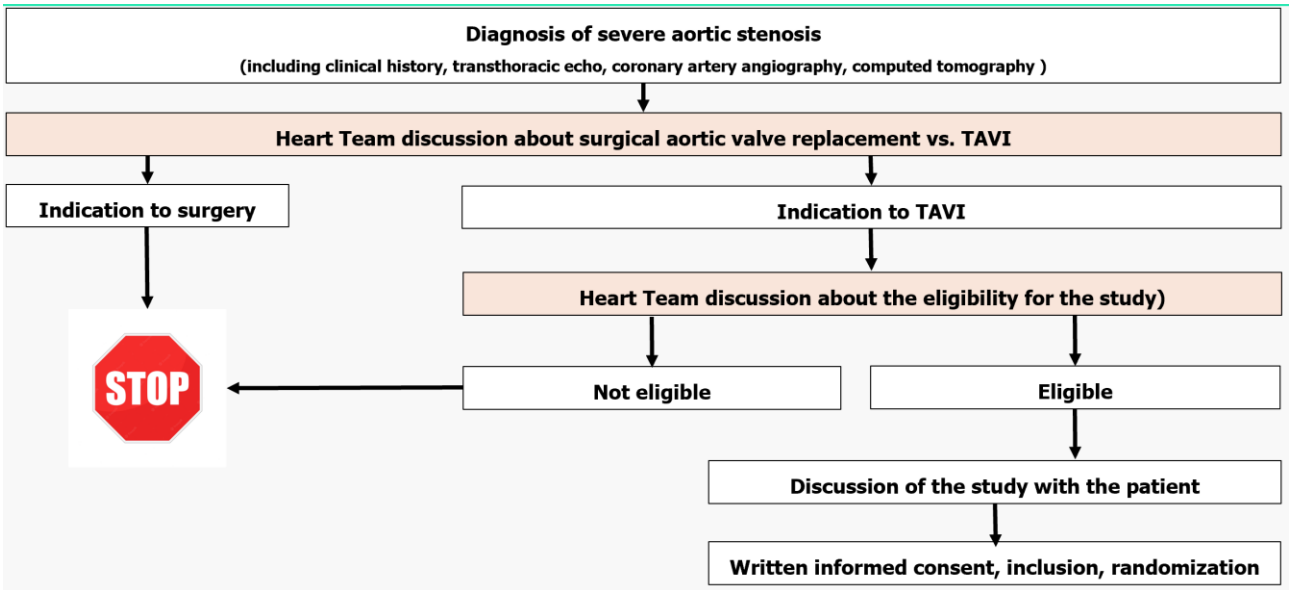


5.2 Identification of the participating centers

The Steering Committee will proceed by inviting potential participating centers. Centers interested in participation must report data regarding organization, activity, and outcome of Heart Team discussion, TAVI selection workflow, collaboration with the referring center with on-site cardiac surgery, waiting time for TAVI, TAVI procedure, TAVI operator experience. The source documents and data will be verified by the DSMB. The DSMB is in charge to accept or not the center for the participation in the study.

5.3 Screening of the patients

The indication to TAVI, the screening of the patients and the eligibility for the study will be performed and shared by the "**Study Heart Team**" of the participating center (see Section 9 for detailed description). After the collection of all the required exams (i.e., transthoracic echocardiography, clinical history, laboratory exams, coronary artery angiography, computed tomography for the assessment of aortic box and vascular accesses), the Study Heart Team will agree with the indication to TAVI. After the indication to TAVI, the Study Heart Team will screen the eligibility for the study. **Eligibility for the study must be agreed and confirmed by all the components of the Study Heart Team**. All the components of the Study Heart Team of the participating center must sign a dedicated eligibility sheet. After Study Heart Team confirmation, the study will be discussed with the patient and relatives (see section 9 for the detailed description).



5.4 Study discussion and informed consent

The study investigator will discuss with the patient and the relatives the study design and procedures. The study investigator will clarify the strengths and limitations of the study. The potential risks related to study

participation will be detailed, as well as the potential alternatives. Only after adequate discussion, the patient will sign the informed consent. Patients can be randomized only after the signature of the informed consent.

5.5 Randomization

Randomization will be performed after the signature of the informed consent. Randomization will be performed centrally using an internet-based system. The patient identification number (Patient ID) and the treatment allocation will be assigned by the central randomization system. Treatment allocation will be assigned according to a computer-generated randomization list stratified by center. Randomization will also be stratified by sex, surgical risk (inoperable vs. other), age (<85 vs. ≥85 years) and valve (self-expandable vs. balloon-expandable). Patients will be randomized to the following:

- EXPERIMENTAL ARM: TAVI WITHOUT ON-SITE SURGERY
- CONTROL ARM: TAVI WITH ON-SITE CARDIAC SURGERY

All patients who are randomized are irrevocably in the study, whether or not they are subsequently found to be eligible, or actually receiving the allocated treatment. Therefore, all patients must be followed until the prespecified study end date.

5.6 Measures to minimize/avoid bias

The trial is open-label. Despite the obvious benefits of a doble-blind design, the hospital where the TAVI intervention is performed cannot be concealed to the operator or the patient. An independent Clinical Event Committee (CEC) will adjudicate all endpoints. The CEC members and the CEC management team will be completely blinded to the randomization, as well as patient identifying information. The CEC will adjudicate the events based on predetermined definitions outlined below (VARC-3 consensus document). Other measures to avoid or minimize bias introduced by the open-label design will include intent-to-treat principles of analysis and use of objective measures for endpoint classification. An additional bias can be that some patients may receive a valve type different from that declared at the time of the randomization. This bias may occur as a consequence of factors and/or variables that emerged after randomization and immediately before the procedure or during the procedure itself. Being crucial that the distribution of self-expandable or balloon-expandable valves would be similar between study groups (despite current literature not reporting significant difference in the outcomes in the comparison of self-expandable vs. balloon-expandable), these data will be strictly monitored and eventual correction to the randomization list will be applied to avoid any unbalance. The Academic Research Organization staff will monitor the type and brand of the valve. This activity will be independent and with the aim of guaranteeing the equal distribution of valves between study arms. Any potential bias and difference will be reported by the ARO team to DSMB, which will be in charge to decide and to suggest possible corrective maneuvers.

6 STUDY POPULATION

6.1 Inclusion criteria

3. Severe aortic stenosis
4. Indication to TAVI confirmed by the Study Heart Team

AND one of the following:

4. Inoperable due to prohibitive operative risk *****
5. High surgical risk as defined as STS score >8% *****
6. The presence of at least one clinical factor compromising the benefit/risk ratio in the case of emergent cardiac surgery *****:
    - Porcelain aorta or severely atherosclerotic aorta
    - Frailty/Reduced physical performance
    - Cognitive impairment, dementia, or Parkinson's disease
    - Severe liver disease/cirrhosis
    - Hostile chest
    - Internal mammalian artery or other critical conduit(s) crossing midline and/or adhering to the posterior table of the sternum
    - Severe pulmonary hypertension and/or severe right ventricular dysfunction
    - Age ≥85 years
    - Severe Chronic Obstructive Pulmonary Disease (COPD)

***: It is mandatory for the inclusion in the study that the Study Heart Team confirm by unanimous judgment the eligibility of each single patient. As described below, it is in charge of the Study Heart Team to weight the feasibility and eventual efficacy of emergent cardiac surgery and based on this assessment to proceed with the eligibility. If the Study Heart estimates the emergent cardiac surgery feasible and potentially effective, the patient cannot be considered eligible.**

6.2 Exclusion criteria

1. Unsuitable for transfemoral TAVI
2. Emergent TAVI
3. Noncardiovascular comorbidity reducing life expectancy to <1 year
4. Any factor precluding 1-year follow-up
5. Refusal of informed consent

7 STUDY PROCEDURES

7.1 Experimental arm: TAVI without on-site surgery

After randomization, the study TAVI operators of the participating center will schedule the patient for TAVI in their hospital without on-site surgery.

7.2 Experimental arm: TAVI with on-site surgery

After randomization, the patient will immediately be placed on the waiting list of the referring center with on-site surgery. The study TAVI operators of the participating center will perform the TAVI procedure in the hospital with on-site surgery according to the waiting list schedule of the latter.

7.3 General information regarding TAVI procedure

TAVI procedure will be performed in accordance with current guidelines and institutional standards. TAVI procedure will be performed by the study TAVI operators. The decision regarding site access management, valve type and size will be left to study TAVI operators. The monitoring after the TAVI procedure and the subsequent mobilization and management of the patient will be in accordance with current guidelines and institutional standards.

7.4 Data collection and Case Report Form

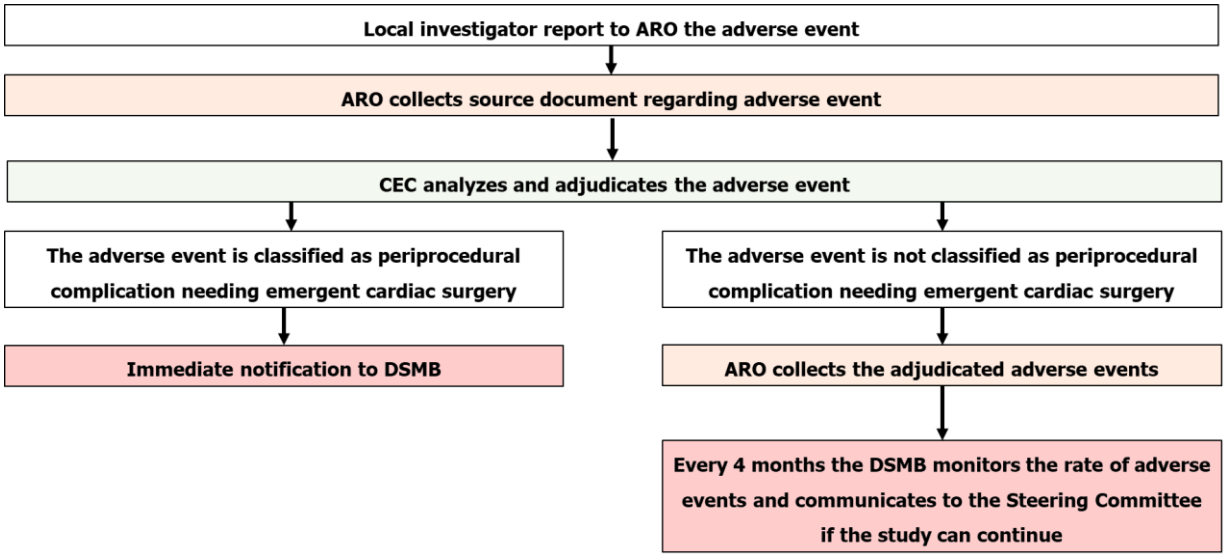
The study investigators will be monitored for consecutive recruitment of patients. A registry of excluded patients will be updated monthly and if selection bias is noticed, it would lead to the exclusion of the center from the investigation. Data will be collected in electronic case report forms (eCRF). The eCRF will be web-based and all investigators will receive specific credentials for the access. The eCRF will also include the web-based tool for randomization. The quality of the data included in the eCRF will be reviewed by the Academic Research Organization (ARO) of the University Hospital of Ferrara. The eCRF will contain a dedicated tool to report adverse events.

7.5 Follow-up

After hospital discharge, routine clinic follow-up will occur at 1, 6, 12 months and then yearly thereafter up to 3 years. At each visit, clinical outcomes, compliance with medical therapy, and quality of life (EQ-5D) will be assessed.

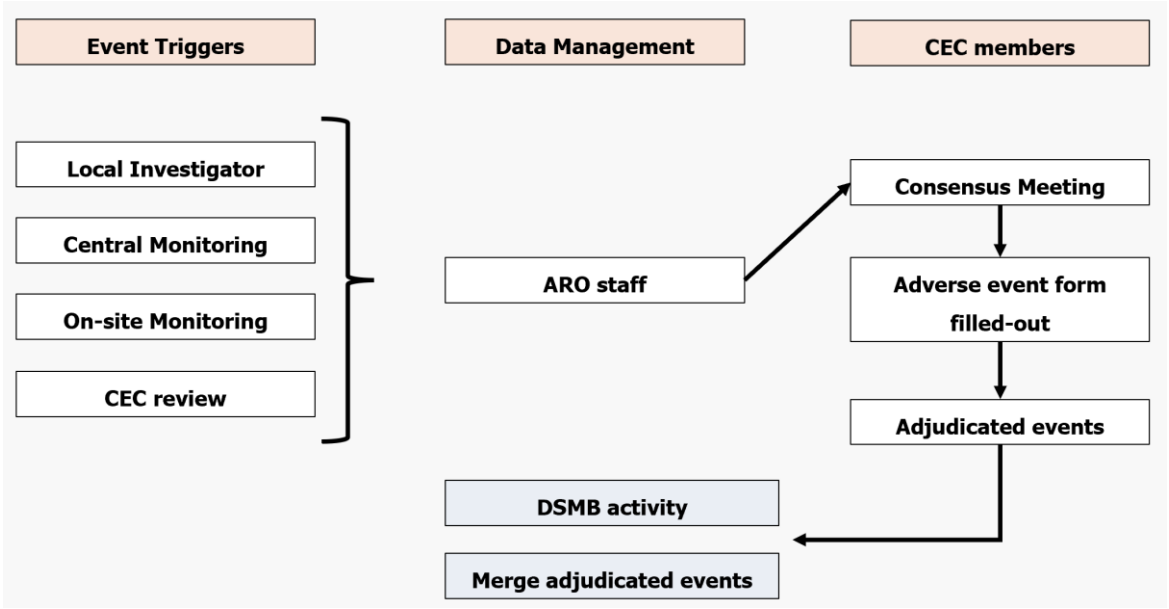
7.6 Study collection of adverse events

All adverse events must be reported by the study investigators. The Academic Research Organization will collect the source document of all adverse events. Adverse events will be adjudicated by the Clinical Event Committee (CEC). As reported below, the CEC will transfer to DSMB the adverse events.



7.7 Adjudication of clinical events

A committee consisting of clinicians who are blinded to treatment allocation will adjudicate all adverse events. The functioning rules and the membership of the Adjudication Committee are detailed in the Adjudication Committee Charter before the start of the trial. The adjudication results will be binding for the final analysis.



7.8 Role of the Data Safety Monitoring Board (DSMB)

The DSMB is responsible for the following items:

- Approval of the participating centers
- Approval of the study TAVI operators
- Analysis of the rate of adverse events in the study arms
- Monitoring of study conduction and of the distribution of valve type and valve brand between study arms

The DSMB is responsible for immediately stopping the trial if the rate of adverse events would be higher than expected. DSMB will strictly monitor the rate of periprocedural complications that require emergent cardiac surgery in the experimental arm and the rate of adverse events while on the TAVI waiting list in the control arm.

Based on previous studies, we assume that the rate of periprocedural complications requiring emergent cardiac surgery should not exceed 2% (minimum number of patients for the analysis n=75), whereas the rate of adverse events during the waiting time for TAVI in the control arm should not exceed 15% (minimum number of patients for the analysis n=100). Anyway, the DSMB:

- will be immediately informed after each periprocedural complication requiring emergent cardiac surgery
- will generate a report each 4 months illustrating the trend of adverse events (in line with or not with the expectations)
- will communicate each 4 months to the Steering Committee if the study can continue or not.

8 STUDY DEFINITIONS

8.1 Requirements for participating centers

Participating centers must be centers without on-site cardiac surgery that meet the following criteria:

1. Availability of standard operating procedure with a cardiac surgery department for an established, weekly Heart Team discussion
2. Availability of standard operating procedure for rapid transfer of patients with procedural complications to cardiac surgery with a maximum delay of 60 minutes (maximum distance between centers without cardiac surgery and referring center 90 km)
3. Five-year experience in screening, selection, and management of TAVI patients
4. At least 2 certified operators or a dedicated intercenter team performing TAVI procedure (see below section “requirements for study TAVI operators”)
5. At least 3 years of experience performing TAVI procedures in a center with on-site cardiac surgery, with participation (as equipe) in at least 100 TAVI procedures.
6. At least 5-year experience in advanced cardiac imaging including transesophageal echocardiography and cardiac computed tomography
7. On-site vascular surgery or on-site availability of certified surgeon and operating room allowing the surgical treatment of vascular complications
8. On-site electrophysiology laboratory (permanent pacemaker implantation)

8.2 Requirements for study TAVI operators

Participating centers must have at least two experienced TAVI operators or a dedicated intercenter team performing TAVI. Operators or teams will work in the same modality on both arms.

The study of TAVI operators must respect the following criteria:

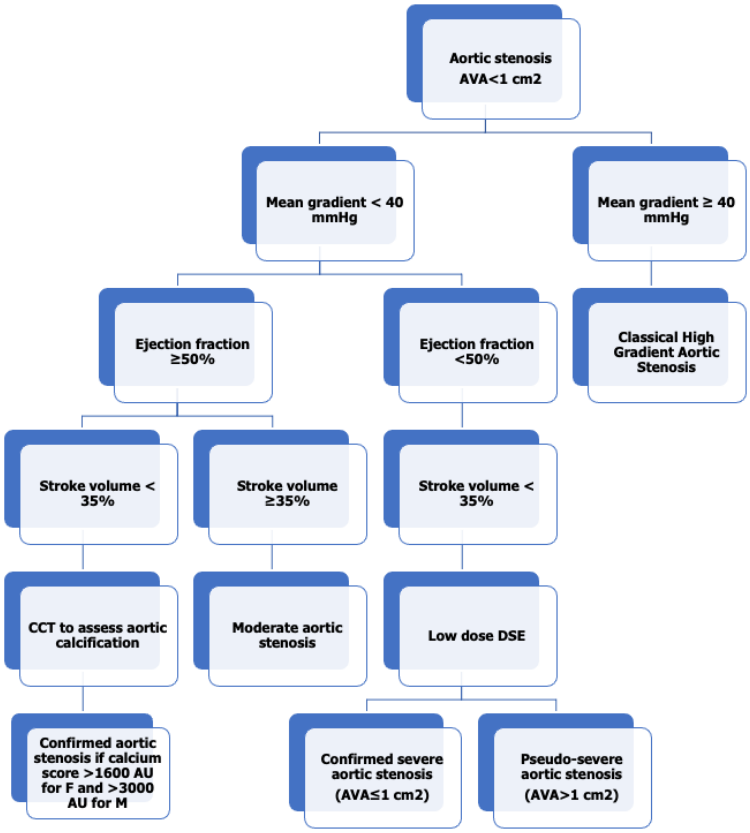
1. At least 5-year experience in coronary interventions
2. More than 75 PCIs by year
3. Experience in the use of tools for the retrieval of intravascular foreign bodies
4. Experience in pericardiocentesis
5. Experience with ultrasound-guided puncture of the femoral artery
6. Experience in suture-mediated closure of femoral artery access
7. Experience in the management of peripheral vascular complications
8. At least 2 years of experience in TAVI procedures as first and second operator
9. At least 50 TAVI procedures as first operator
10. More than 20 TAVI by year.

8.3 Severe aortic stenosis

The diagnosis of aortic stenosis will be made with an echocardiographic evaluation according to the current guidelines as follows [8]:

- Classical- high gradient aortic stenosis: mean trans-valvular gradient ≥ 40 mmHg, valve area <1 cm^2 (or < 0.6 cm2/m^2), peak velocity≥ 4 m/s independently by ejection fraction and stroke volume.
- Low-flow low-gradient aortic stenosis: mean trans-valvular gradient < 40 mmHg, valve area <1 cm^2, ejection fraction <50% and stroke volume < 35 ml/m^2. Low dose dobutamine stress echocardiography is recommended to distinguish between true low-flow low gradient aortic stenosis and pseudo-severe aortic stenosis (increase in valve area>1 cm^2 with increase in stroke volume).
- Paradoxical low-flow low-gradient aortic stenosis: mean trans-valvular gradient < 40 mmHg, valve area <1 cm^2, ejection fraction ≥50% and stroke volume ≤ 35 ml/m^2). In this case CT scan for calculation of calcium score is recommended to confirm the presence of very likely, likely or unlikely aortic stenosis (respectively value of >1600; >1200 and <800 Agaston units for female and >3000; > 2000 and <1600 Agaston units for male.
- Normal flow-low gradient aortic stenosis: mean trans-valvular gradient < 40 mmHg, valve area <1 cm^2, ejection fraction >50% and stroke volume ≥ 35 ml/m^2. This is usually a moderate aortic stenosis.

The Figure below summarizes the criteria for the diagnosis.



8.4 Risk scores

The EuroSCORE and the Society of Thoracic Surgeons (STS) score are the most widely used risk scores to predict operative mortality in cardiac surgery. **These models were developed and validated in a standard surgical risk population. Therefore, the predictive power of both models is suboptimal in high-risk patients with valvular disease.** The STS score has been shown to outperform the Logistic EuroSCORE II. Scores can be calculated online with dedicated calculators:

- http://riskcalc.sts.org/stswebriskcalc/calculate
- http://www.euroscore.org/calc.html

Surgical mortality risk strata are difficult to precisely assign, but an estimated 30-day mortality of <4% is considered low risk, 4–8% is intermediate risk, and >8% is high risk. Although all enrolled patients will undergo a Risk Score evaluation, this score will be integrated by clinical judgement. In fact, a patient is considered inoperable if the cardiovascular surgeons of the Heart Team deny surgery due to a prohibitive operative risk. Anyway, current scores do not include specific clinical and anatomical variables that strongly affect the mortality and the decision making between aortic valve replacement vs. TAVI. Some examples are a porcelain aorta, frailty, reduced physical performance, cognitive dysfunction, or advanced age (>85 years).

8.5 TAVI workflow

Before Heart Team discussion, patients should be evaluated with the following tests and parameters in agreement with current guidelines.

- Echocardiography

Echocardiography is the key to confirm the diagnosis and severity of aortic stenosis, assessing valve calcification, LV function, and wall thickness, detecting other valve disease or aortic pathology, and providing prognostic information. Assessment should be undertaken when blood pressure (BP) is well controlled to avoid the confounding flow effects of increased afterload. Current international recommendations for the echocardiographic evaluation of patients with aortic stenosis depend upon measurement of the mean pressure gradient (the most robust parameter), peak transvalvular velocity (Vmax), and valve area.

- Quantification of valve calcification

Quantification of valve calcification predicts disease progression and clinical events and may be useful when combined with geometric evaluation of the valve area to assess the severity of aortic stenosis in patients with low valve gradient

- Coronary angiography

Coronary angiography is essential before TAVI and SAVR to determine the potential need for concomitant revascularization. Retrograde LV catheterization is not recommended unless there are symptoms and signs of severe aortic stenosis and noninvasive investigations are inconclusive.

- Cardiac computed tomography (CCT)

CCT is the preferred imaging tool to assess: (i) aortic valve anatomy, (ii) annular size and shape, (iii) extent and distribution of valve and vascular calcification, (iv) risk of coronary ostial obstruction, (v) aortic root dimensions, (vi) optimal fluoroscopic projections for valve deployment, and (vii) feasibility of vascular access (femoral, subclavian, axillary, carotid, transcaval or transapical). Adverse anatomical findings may suggest that SAVR is a better treatment option. CCT is mandatory in patients with indication of TAVI and is mandatory before the Heart Team discussion for study eligibility. CCT scans will be collected and re-analysed by an independent core lab.

8.6 Study Heart Team: composition

Each participating center must identify the "**Study Heart Team**".

The Study Heart Team consists of:

- Study TAVI operator(s)
- Cardiovascular surgeon of the referring center
- Cardiac imaging specialist
- Clinical cardiologists

Anyway, its composition is dynamic and can also include TAVI operators of the referring center with on-site cardiac surgery, anesthesiologists, geriatricians, neurologists, etc. This multidisciplinary team convenes as a group on a regular basis to review and analyze clinical data to reach consensus on the optimal treatment strategy for each patient.

The Study Heart Team has two different important functions in the study that must be maintained separated in the study flow and patient management: the first is to share the indication to TAVI about surgical aortic valve replacement, the second is to confirm the eligibility of each single patient for the study.

8.7 Study Heart Team: Indication to TAVI

The following information regarding each single patient will be analyzed and discussed:

- General medical history with major comorbidity (in particular: assessment of disease limiting life expectancy < 1 year; chronic kidney disease; severe peripheral artery disease)
- Medical therapy
- Frailty assessment (with geriatric assessment and estimation of overall quality of life)

- Concomitant cardiac conditions requiring intervention: coronary artery disease requiring revascularization; severe concomitant mitral or tricuspid regurgitation; severe septal hypertrophy; aortic aneurisms
- Anatomical and procedural factors: TAVI feasible by transfemoral approach (or by other approaches); sequelae of chest radiation; porcelain aorta; high likelihood of severe patient prosthesis mismatch (AVA<0.65 cm2/m2); severe chest deformation or scoliosis; aortic annular dimensions for the choice of TAVI valve (dimensions and model); aortic valve morphology (bicuspid aortic valve, severe calcification in left ventricle outflow-tract or of the leaflet); position of coronary ostia (to check for risk of coronary obstruction in case of low coronary ostia); presence of thrombus is aorta or in left ventricle.

The decision to proceed with TAVI must be reached with consensus of the entire Study Heart Team for all patients.

8.8 Study Heart Team: Assessment of TAVI futility

Advancements in innovation and technology have equipped us with the ability to successfully treat patients suffering the most advanced stages of AS who have traditionally been deemed inoperable or too high-risk for conventional SAVR. Despite enthusiasm for high rates of device-related procedural success, the success of monitored anesthesia care without the need for endotracheal intubation, and relatively low rates of procedural mortality, the sobering reality is that a substantial portion of these individuals fail to derive long-term functional improvement post-TAVI. The current protocol is focused on patients with indication to TAVI inoperable or at high surgical risk. The main role of the Heart Team is to discriminate patients with a higher probability of futility of the TAVI procedure. Anyway, no standardized definition is available and in particular predictor of poor prognosis significantly varies across studies. The study Heart Team in the assessment before TAVI indication will consider the risk of futility. In particular, the study Heart Team will consider:

- PARTNER TAVI score [27]
- FRANCE 2 TAVI score [28]
- Frailty assessed by Katz index and Essential Frailty toolset (EFT) [29]
- Major organ compromise that cannot be improved by TAVI

Based on this information, the study Heart Team will decide to declare futile the procedure or to proceed to TAVI procedure and then to consider the eligibility to the study.

Criteria	Low risk	Intermediate risk	High risk	Prohibitive risk
PARTNER TAVI score[a], OR FRANCE 2 TAVI score	<25% risk of mortality or lack of QOL improvement at 6 months Risk score: 0 (30-day mortality risk < 5%)	25–50% risk of mortality or lack of QOL improvement at 6 months Risk score: 1–5 (30-day mortality risk 5–15%)	>50% risk of mortality or lack of QOL improvement at 6 months Risk score: 6–7 (30-day mortality risk 15–25%)	Risk score ≥ 8 (30-day mortality risk > 25%)
Frailty[b]	None	1 index	≥2 indices	≥4 indices
Specific major organ system compromise not to be improved post-TAVI[c]	None	1 organ system	2 organ systems	≥3 organ systems

[a]http://h-outcomes.com/tavi-risk-calculator/.
[b]Frailty based on Katz Index (independence in feeding, bathing, dressing, transferring, toileting, and urinary incontinence)[30] and independence in ambulation (walk 5 m in <6 s).
[c]Examples of major organ system compromise:[34] Cardiac—severe LV systolic or diastolic dysfunction or RV dysfunction, and fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV1 < 50% or DLCO < 50% of predicted; CNS dysfunction (dementia, Alzheimer's disease, Parkinson's disease, and CVA with persistent physical limitation); GI dysfunction—Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin < 3.0; cancer—active malignancy; and liver—any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy.

8.9 Study Heart Team: eligibility of the patient for the study

For each patient with indication to TAVI, the Study Heart Team will analyze with caution two different macro categories of factors:

i. **factors that preclude emergent cardiac surgery or are associated with high mortality despite emergent cardiac surgery,**
ii. **factors that significantly increase the probability of emergent cardiac surgery and that can be solved by emergent cardiac surgery.**

The presence of the first macro category of factors is important to support the eligibility for the study of the patient. On the contrary, the second macro category of factors is important to discourage eligibility for the study of the patient. Therefore, the evaluation of the Study Heart Team will not only be based on the STS score but will consider a list of factors and will achieve agreement on the eligibility or not of each patient. A dedicated "Study Heart Team eligibility form" will be filled and signed for each single patient. ***It is mandatory for the inclusion in the study that the Study Heart Team confirms by unanimous judgment the eligibility of each single patient. No patient can be randomized if only one member of the Study Heart team disagrees.***

The Table below summarizes the main factors that the Study Heart Team should consider for eligibility in addition to the STS score value.

Factors compromising the benefit/risk ratio in the case of emergent cardiac surgery	
Porcelain aorta or severely atherosclerotic aorta	Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible

Frailty/Reduced physical performance	Slowness, weakness, exhaustion, waste and malnutrition, poor endurance and inactivity, loss of independence Criteria: • 5 m walking time • Grip strength • BMI <20 kg/m^2 and/or weight loss 5 kg/year
Cognitive impairment, dementia, or Parkinson's disease	Based on the geriatrician's assessment
Severe liver disease/cirrhosis	Any of the following: • Child-Pugh class C • MELD score ≥10 • Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt • Biopsy-proven cirrhosis with portal hypertension or hepatocellular dysfunction
Hostile chest	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal anatomy of the chest wall due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications of previous surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis, or esophageal stricture) • History of multiple recurrent pleural effusions that cause internal adhesions
Internal mammalian artery (IMA) or other critical conduit(s) crossing the midline and/or adherent to the posterior table of the sternum	A patent IMA graft that is adherent to the sternum such that it is likely to be injured during reoperation. A patient may be considered at extreme risk if any of the following is present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum • The conduit(s) are radiographically distinguishable from the posterior table of the

	sternum but lie within 2–3 mm of the posterior table
Severe pulmonary hypertension and/or severe right ventricular dysfunction	Criteria as defined by the guidelines
Age ≥85 years	
Severe Chronic Obstructive Pulmonary Disease (COPD)	VEV1<60%, reduced DLCO, home-oxygen
Factors increasing the probability of emergent cardiac surgery	
Extreme aorta tortuosity	It is based on CCT analysis, and it should be associated with a higher risk of aortic dissection during the TAVI procedure
Very low coronary ostia	Anatomical condition should be associated with a significant risk of coronary obstruction without an adequate possibility to guarantee protection with percutaneous techniques
Left ventricle of reduced dimension and/or with a large area of fibrosis (scar)	It should be associated with a significant increase in the probability of perforation of the left ventricle
Severe calcification of the calcium nodule in the left ventricle outflow tract or of the leaflet	It should be associated with a significant increase in the probability of perforation of the aortic annulus
Extra-large (≥683 mm2 or ≥94.2 mm) aortic annuli	It should be associated with a significant increase in valve malposition or embolization

8.10 Clinical endpoints

Clinical adverse events of interest are defined in agreement with the consensus documents of the Valve Academic Research Consortium (VARC)-2 and VARC-3 and are described in the following [10, 30]. **It should be noted that the primary endpoint of the study has been selected in agreement with the suggestions of the VARC-3 consensus document that stated that the best composite endpoint of 1 year is that that combines all-cause mortality, stroke, and hospitalization for procedure or valve-related cardiovascular causes.**

Clinical efficacy (at 1 year and thereafter)

- Freedom from all-cause mortality
- Freedom from all stroke
- Freedom from hospitalization for procedure- or valve-related causes
- Freedom from KCCQ Overall Summary Score <45 or decline from baseline of >10 point (i.e. Unfavourable Outcome)

8.11 Mortality

TABLE 2 Mortality*

Causes of mortality
All-cause mortality
Cardiovascular mortality
Death meeting one of the following criteria: ■ Related to heart failure, cardiogenic shock, bioprosthetic valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (e.g. mediastinitis, endocarditis), or other clear cardiovascular cause ■ Intraprocedural death ■ Sudden death ■ Death of unknown cause
Valve-related mortality
Death presumed to be related to bioprosthetic valve dysfunction†
Non-cardiovascular mortality
Death clearly related to a non-cardiovascular cause: such as respiratory failure *not* related to heart failure (e.g. pneumonia), renal failure, liver failure, infection (e.g. urosepsis), cancer, trauma, and suicide
Timing of mortality
Periprocedural mortality
Death meeting one of the following criteria: ■ Occurring ≤30 days after the index procedure ■ Occurring >30 days but during the index hospitalization‡
Early mortality
Death occurring >30 days but ≤1 year after the index hospitalization
Late mortality
Death occurring >1 year after the index hospitalization

8.12 Hospitalization for cardiovascular cause

It is defined as any non-elective admission to the hospital after randomization and before the end of follow-up. If patients are admitted more than once, each admission will be collected as a single event.

Readmission is defined for cardiovascular cause, in agreement with the VARC-3 consensus. **The VARC-3 consensus document suggests considering hospitalization related to the procedure or valve at one year of follow-up. Anyway, the present protocol is focused not only on the follow-up after the TAVI procedure, but also on the waiting time between randomization and the TAVI procedure. For this reason, in the primary endpoint will be considered both procedure-related or valve-related hospitalization and other cardiovascular hospitalization (hospitalization for cardiovascular cause = cardiovascular hospitalization).**

TABLE 4 Hospitalization (or re-hospitalization)

Definition
Any admission after the index hospitalization or study enrolment to an inpatient unit or hospital ward for ≥24 h, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition. Visits to urgent care centres or emergency departments <24 h may also be included if substantive intensification of therapy changes (e.g. heart failure episodes) are enacted (e.g. intravenous diuretics, significant increases in drug therapy dosages or addition of new pharmacotherapy agents)
Categories of hospitalization
Cardiovascular hospitalization
Procedure-related or valve-related hospitalization ■ ***Hospitalization for new complications*** such as stroke, bleeding (e.g. haemothorax, retroperitoneal haematoma), pericardial effusion, vascular or access-site complication (e.g. limb ischaemia, wound infection), new conduction disturbance or arrhythmia (e.g. atrioventricular block, atrial fibrillation), acute kidney injury, or any other procedure-related new complication, including periprocedural valve-related heart failure (e.g. paravalvular leak, worsening LV function, worsening sub-valvular obstruction) ■ ***Exacerbation or deterioration of previous in-hospital periprocedural complication*** (e.g. ventilator-induced pneumonia, recurrent pericardial or pleural effusion, recurrent haemothorax, valve-related heart failure) ■ ***Bioprosthetic valve dysfunction**** such as valve thrombosis, endocarditis, structural valve deterioration, or non-structural valve dysfunction ■ ***Untreated diseased native aortic valve†*** or its related consequences such as heart failure, syncope, angina, new-onset arrhythmia, endocarditis, or any other symptoms or consequences related to the untreated native aortic valve ■ ***Bleeding complications related to oral anticoagulation or antiplatelet therapy*** for valve-related thromboembolic prevention or atrial fibrillation ■ ***Heart failure-related hospitalizations‡*** requiring that new or worsening heart failure be the predominant reason for a hospital stay ≥24 h on the basis of symptoms and signs of heart failure with confirmation by diagnostic tests and necessitating treatment using intravenous or mechanical heart failure therapies. Includes primary (cardiac related) and secondary (non-cardiac related)
Other cardiovascular hospitalization ■ ***Cardiovascular hospitalization not directly related to the index procedure or the untreated native aortic valve***
Including: acute myocardial infarction or chronic coronary artery disease, hypertension, arrhythmia (not related to the procedure or aortic valve), heart failure from other specific and proven aetiologies (e.g. cardiomyopathies, concomitant untreated non-aortic valvular disease, severe right ventricular dysfunction), peripheral vascular disease
Non-cardiovascular hospitalization ■ ***Hospitalization not due to cardiovascular causes as defined above***
Including: non-cardiovascular infection and sepsis (e.g. urosepsis), respiratory failure that is not related to heart failure (e.g. pneumonia), renal failure, liver failure, delirium or dementia, cancer, trauma, or psychiatric illness

A separate prespecified analysis will be performed in hospitalizations that occur between randomization and TAVI. In particular, hospitalization for heart failure or emergent aortic balloon valvuloplasty will be strictly monitored and considered for dedicated subanalyses.

8.13 Periprocedural complications actionable by emergent cardiac surgery

Valve Academic Research Consortium 3 introduces a new category of complications deemed to capture and classify injury of any cardiac structure occurring during the procedure.

TABLE 7 Cardiac structural complications

Major

One of the following:

- Cardiac structure* perforation, injury, or compromise resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
- New pericardial effusion resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
- Coronary obstruction† resulting in death, haemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention. Coronary obstruction may be acute (during the procedure) or delayed (after completion of the procedure).
- Coronary artery access difficulties for needed coronary angiography or intervention, resulting in death, haemodynamic compromise, myocardial infarction, coronary or aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure

Minor

One of the following:

- Cardiac structure* perforation, injury, or compromise *not* resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
- New pericardial effusion *not* resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
- Coronary obstruction *not* resulting in death, haemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention
- Coronary artery access difficulties for needed coronary angiography or intervention, *not* resulting in death, haemodynamic compromise, myocardial infarction, coronary or aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure

*Aortic annulus, left ventricular outflow tract, ventricular septum, left or right ventricle, atrial septum, left or right atrium, mitral valve apparatus, tricuspid valve apparatus, coronary artery, and coronary sinus. Also includes any new inter-cardiac cavity communication (e.g. VSD), and new left-to-right or right-to-left shunt.

†Angiographic or echocardiographic evidence of a new partial or complete obstruction of a coronary ostium or an epicardial coronary artery, either by the valve prosthesis itself, the native leaflets, embolized material (e.g. calcification, thrombus, and/or tissue), external device compression, or the consequence of coronary artery instrumentation (e.g. dissection, occlusion, embolization), occurring during or after the procedure, and with objective evidence of ischaemia (i.e. new ST-segment deviation on electrocardiogram) or symptoms. Excludes coronary complications due to a concomitant or subsequent planned percutaneous intervention for significant coronary artery disease.

TABLE 8 Other acute procedural and technical valve-related complications*

Conversion to open surgery

Conversion to open sternotomy or thoracotomy using cardiopulmonary bypass secondary to any procedure-related complication or failed intended transcatheter approach. Should be classified as:

- *Intraprocedural conversion:* during the index procedure
- *Periprocedural conversion:* ≤30 days after the index procedure
- *Delayed conversion:* >30 days after the index procedure

Unplanned use of mechanical circulatory support†

Implantation of multiple (>1) transcatheter valves during the index hospitalization

Valve malposition

Should be classified as:

- *Valve migration:* After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, without valve embolization
- *Valve embolization:* The valve prosthesis moves either upward or downward after final deployment such that it loses contact with the aortic annulus
- *Ectopic valve deployment:* Irretrievable deployment of a valve prosthesis at a site other than the intended position because of valve embolization or inability to deliver the prosthesis to the desired location

Paravalvular regurgitation (see Table 16)

*Individual events should be collected so that specific event rates can be determined.
†Mechanical circulatory support includes: cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), transcatheter pumps (e.g. Impella) or intra-aortic balloon pump (IABP).

For the specific purpose of the present study, the following periprocedural complications that occur in the first 72 hours after TAVI are considered actionable by emergent cardiac surgery:

- Severe aortic regurgitation with clinical instability
- Valve embolization into the left ventricle
- Valve migration with concomitant and refractory haemodynamic instability
- Aortic dissection
- Aortic perforation
- Aortic rupture
- Annular rupture
- Perforation of the left ventricle
- Coronary obstruction (that cannot be managed by percutaneous intervention)
- Ventricular septal perforation
- New damage (chordae papillary muscle, or leaflet) to the mitral valve apparatus or dysfunction (e.g., restrictions due to THV) of the mitral valve.

8.14 Emergent cardiac surgery for periprocedural complications

It is defined as any cardiothoracic surgical intervention with cardiopulmonary bypass for periprocedural complications (see paragraph 8.13) requiring urgent aortic valve replacement, repair of myocardial or aortic injury, or pericardial drainage performed within the first 72 hours after TAVI.

8.15 Death due to periprocedural complications actionable by emergent cardiac surgery

It is defined as any death associated with periprocedural complications actionable by emergent cardiac surgery (see paragraphs 8.13 and 8.14). The occurrence of this endpoint will be considered both in cases where emergent cardiac surgery was not performed and in cases where it is performed but with lethal outcome.

8.16 Myocardial infarction

TABLE 11 Myocardial infarction (adapted from 4th Universal, SCAI and ARC-2 definitions)

Type 1 (Spontaneous MI) (>48 h after the index procedure)*
- Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL with at least one of the following:
  - Symptoms of acute ischaemia
  - New ischaemic ECG changes (new ST-segment or T-wave changes or new LBBB)
  - New pathologic Q-waves in ≥2 contiguous leads
  - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality in a pattern consistent with an ischaemic aetiology
  - Identification of a coronary thrombus by angiography or autopsy
- Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values

Type 2 (Imbalance between myocardial oxygen supply and demand)*
- Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:
  - Symptoms of ischaemia
  - ECG changes indicative of new ischaemia (new ST-segment or T-wave changes or new LBBB)
  - New pathologic Q-waves in ≥2 contiguous leads
  - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

Type 3 (MI associated with sudden cardiac death)*
- Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Type 4A (Criteria for PCI-related MI ≤48 h after the index procedure)†
- ***In patients with normal baseline CK-MB:*** The peak CK-MB measured within 48 h of the procedure ≥10× the local laboratory ULN or CK-MB ≥5× ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
  - New persistent LBBB‡
  - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
  - Substantial new loss of viable myocardium on imaging related to the procedure
- In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70× the local laboratory ULN or ≥35× ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
  - New persistent LBBB‡
  - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
  - Substantial new loss of viable myocardium on imaging related to the procedure
- ***In patients with elevated baseline CK-MB (or cTn):*** The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.

Type 4B (Stent thrombosis)*
- Stent thrombosis as documented by angiography or autopsy using the same criteria utilized for type 1 MI.
  - Acute: 0 to 24 h
- Subacute: >24 h to 30 days
- Late: >30 days to 1 year
- Very late: >1 year after stent implantation

Type 4C (Coronary stent restenosis)*
- Focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI

Type 5 Periprocedural (post-SAVR, TAVR or CABG) MI (≤48 h after the index procedure)†
- ***In patients with normal baseline CK-MB:*** The peak CK-MB measured within 48 h of the procedure ≥10× the local laboratory ULN or CK-MB ≥5× ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
- New persistent LBBB‡
- Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
- Substantial new loss of viable myocardium on imaging related to the procedure
- In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70× the local laboratory ULN or ≥35× ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
- New persistent LBBB‡
- Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
- Substantial new loss of viable myocardium on imaging related to the procedure
- ***In patients with elevated baseline CK-MB (or cTn):*** The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.

The use of high-sensitivity (hs)-troponins is recommended for diagnosis of spontaneous MI, but has not been studied for assessment of periprocedural MI. Standard troponin assays are therefore recommended for evaluation of periprocedural MI. Periprocedural biomarker elevation >ULN not meeting the criteria for MI should be categorized as 'myocardial injury not meeting MI criteria'.

*Adapted from Thygesen *et al.* (169).

†Adapted from Moussa *et al.* (167) and Garcia-Garcia *et al.* (168).

‡LBBB criteria to be used with caution after TAVR or SAVR given the relatively high rate of new LBBB after these procedures.

CK-MB = creatine kinase-MB; cTn, cardiac troponin; ECG = electrocardiogram; LBBB = left bundle branch block; MI, myocardial infarction; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; ULN = upper limit of normal; URL = upper reference limit.

8.17 Stroke (cerebrovascular accident)

TABLE 3 Neurologic events

Categories of neurologic events
Overt CNS injury (NeuroARC Type 1)
All stroke*
■ *Ischaemic stroke*† Acute onset of focal neurological signs or symptoms conforming to a focal or multifocal vascular territory within the brain, spinal cord, or retina (NeuroARC Type 1a or 1aH) and fulfilling one of the following criteria: ■ Signs or symptoms lasting ≥24 h or until death, with pathology or neuroimaging evidence of CNS infarction, or absence of other apparent causes ■ Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory‡ ■ *Haemorrhagic stroke* Acute onset of neurological signs or symptoms due to intracranial bleeding from intracerebral or subarachnoid haemorrhage not due to trauma (NeuroARC Types 1b or 1c) ■ *Stroke, not otherwise specified* Acute onset of neurological signs or symptoms persisting ≥24 h or until death but without sufficient neuroimaging or pathology evidence to be classified (NeuroARC Type 1d)
Symptomatic hypoxic-ischaemic injury Non-focal (global) neurological signs or symptoms with diffuse brain, spinal cord, or retinal cell death confirmed by pathology or neuroimaging and attributable to hypotension or hypoxia (NeuroARC Type 1e)
Covert CNS injury (NeuroARC Type 2)
Covert CNS infarction‡ or haemorrhage Neuroimaging or pathological evidence of CNS focal or multifocal ischaemia (NeuroARC Type 2a or 2aH) or haemorrhage (NeuroARC 2b) *without* acute neurological symptoms consistent with the lesion or bleeding location
Neurologic dysfunction (acutely symptomatic) without CNS injury (NeuroARC Type 3)
TIA Transient focal neurological signs or symptoms lasting <24 h presumed to be due to focal brain, spinal cord, or retinal ischaemia, but *without* evidence of acute infarction by neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3a or Type 3aH)
Delirium without CNS injury Transient non-focal neurological signs or symptoms, typically of variable duration, *without* evidence of infarction on neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3b)
Stroke grading*
Acute stroke severity§ ■ *Mild neurological dysfunction*: NIHSS 0-5 ■ *Moderate neurological dysfunction*: NIHSS 6-14 ■ *Severe neurological dysfunction*: NIHSS ≥15
Stroke disability‖ ■ *Fatal Stroke:* death resulting from a stroke ■ *Stroke with disability:* mRS score of ≥2 at 90 days‖ *and* increase of ≥1 from pre-stroke baseline ■ *Stroke without disability:* mRS score of 0 (no symptoms) or 1 (able to carry out all usual duties and activities) at 90 days‖ or *no* increase in mRS category from pre-stroke baseline
Neurological events timing
■ *Periprocedural:* Occurring ≤30 days after the index procedure ■ Acute: Occurring ≤24 h after the index procedure ■ Sub-acute: Occurring >24 h and ≤30 days after the index procedure ■ *Early:* Occurring >30 days and ≤1 year after the index procedure ■ *Late:* Occurring >1 year after the index procedure

8.18 Bleeding complications

TABLE 5 Bleeding and transfusions*

Overt bleeding† that fulfils one of the following criteria:

Type 1
- Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, leading to hospitalization, an increased level of care, or medical evaluation (BARC 2)
- Overt bleeding that requires a transfusion of 1 unit of whole blood/red blood cells‡ (BARC 3a)

Type 2
- Overt bleeding that requires a transfusion of 2-4 units of whole blood/red blood cells‡ (BARC 3a)
- Overt bleeding associated with a haemoglobin drop of >3 g/dL (>1.86 mmol/L) but <5 g/d (<3.1 mmol/L) (BARC 3a)

Type 3
- Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial (associated with haemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome (BARC 3b, BARC 3c)
- Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring vasopressors or surgery (BARC 3b)
- Overt bleeding requiring reoperation, surgical exploration, or re-intervention for the purpose of controlling bleeding (BARC 3b, BARC 4)
- Post-thoracotomy chest tube output ≥2 L within a 24-h period (BARC 4)
- Overt bleeding requiring a transfusion of ≥5 units of whole blood/red blood cells (BARC 3a) ‡
- Overt bleeding associated with a haemoglobin drop ≥5 g/dL (≥3.1 mmol/L) (BARC 3b).

Type 4
- Overt bleeding leading to death. Should be classified as:
  - ***Probable:*** Clinical suspicion (BARC 5a)
  - ***Definite:*** Confirmed by autopsy or imaging (BARC 5b)

For the current study, the bleeding complications 3a, 3b, 3c, 4, 5a and 5b will be considered.

8.19 Acute kidney injury

TABLE 10 Acute kidney injury*

Stage 1

AKI that fulfils at least one of the following criteria:
- Increase in serum creatinine ≥150-200% (≥1.5-2.0× increase) within 7 days compared with baseline
- Increase of ≥ 0.3mg/dL (≥26.4 µmol/L) within 48 h of the index procedure

Stage 2

AKI that fulfils the following criterion:
- Increase in serum creatinine >200-300% (>2.0-3.0× increase) within 7 days compared with baseline

Stage 3

AKI that fulfils at least one of the following criteria:
- Increase in serum creatinine >300% (>3.0× increase) within 7 days compared with baseline
- Serum creatinine ≥4.0 mg/dL (≥354 µmol/L) with an acute increase of ≥0.5 mg/dL (≥44 µmol/L)

Stage 4

AKI requiring new temporary or permanent renal replacement therapy

Adapted from Clinical Practice Guidelines for Acute Kidney Injury 2012. https://kdigo.org/guidelines/acute-kidney-injury/.

*Given practical challenges with the use of urine output criteria in daily practice, AKI should be solely defined based on serum creatinine values. Acute kidney injury defined by urine output using the following criteria might be used in the context of a dedicated AKI study: AKI Stage 1: Urine output <0.5 mL/kg/h for ≥6 but <12 h; AKI stage 2: Urine output <0.5 mL/kg/h for ≥12 but <24 h; AKI stage 3: Urine output <0.3 mL/kg/h for ≥24 h or anuria for ≥12 h.

AKI = acute kidney injury.

8.20 Vascular access site and access-related complications

TABLE 6 Vascular and access-related complications*

Vascular complications†
Major
One of the following: ■ Aortic dissection or aortic rupture ■ Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) or compartment syndrome resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment ■ Distal embolization (non-cerebral) from a vascular source resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage ■ Unplanned endovascular or surgical intervention resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment ■ Closure device failure‡ resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
Minor
One of the following: ■ Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) *not* resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment ■ Distal embolization treated with embolectomy and/or thrombectomy, *not* resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage ■ Any unplanned endovascular or surgical intervention, ultra-sound guided compression, or thrombin injection, *not* resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment ■ Closure device failure‡ *not* resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
Access-related non-vascular complications
Major
One of the following: ■ Non-vascular structure, non-cardiac structure§ perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention ■ Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention
Minor
One of the following: ■ Non-vascular structure, non-cardiac structure§ perforation, injury, or infection *not* resulting in death, VARC type ≥2, irreversible nerve injury, or requiring unplanned surgery or percutaneous intervention ■ Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection *not* resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention

8.21 Conduction disturbances and arrhythmias

TABLE 9 Conduction disturbances and arrhythmias

Pre-index procedure

- **Conduction disturbances**
  - 1st-degree AV block
  - *2nd-degree AV block*
  - Left bundle branch block
  - Right bundle branch block
  - IVCD with QRS ≥120 ms
  - Bradycardia (heart rate <60 b.p.m.) or SSS
- **Permanent pacemaker**
  - Type of permanent pacemaker should be recorded (e.g. single chamber, dual chamber, biventricular, defibrillator)
- **Atrial fibrillation (or flutter)**
  - Paroxysmal, persistent, long-standing persistent, or permanent

During or after index procedure*

- **Conduction disturbances**
  - 1st-, 2nd-, 3rd-degree AV block
  - Left bundle branch block
  - IVCD with QRS ≥120 ms
  - ***New-onset***: defined as a new conduction disturbance relative to baseline
  - ***Timing of occurrence:*** Procedural: ≤24 h after the index procedure
    Delayed: >24 h after the index procedure
  - ***Duration:*** Transient: resolved before discharge or ≤7 days after the index procedure in case of prolonged hospitalization
    Persistent: present at hospital discharge or >7 days after the index procedure in case of prolonged hospitalization
    Permanent: present >30 days after the index procedure
- **Permanent pacemaker**
  - ***Type:*** single, dual, biventricular, defibrillator, leadless
  - ***Timing:*** No. of days after the index procedure
  - ***Indication:*** including AV Block, SSS
- **Atrial fibrillation (or flutter)**
  - ***New-onset:*** defined as any arrhythmia that was not present at baseline that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG or at least 30 s on a rhythm strip
  - ***Timing of occurrence†:***
    Periprocedural: ≤30 days after the index procedure
    Late/spontaneous: >30 days after the index procedure
  - ***Duration†:***
    Paroxysmal: atrial fibrillation that terminates spontaneously or with intervention ≤7 days of onset.
    Persistent: Continuous atrial fibrillation that is sustained >7 days.
    Long-standing persistent: Continuous atrial fibrillation >12 months in duration.
    Permanent: Used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.

*The calculation of new pacemaker rates should exclude patients with pre-existing pacemaker. The same principle applies to reporting of rates of new conduction disturbances and arrhythmias.
†From January *et al* (136).

AF = atrial fibrillation or atrial flutter; AV = atrioventricular; ECG =, electrocardiogram; IVCD = intraventricular conduction delay; SSS = sick sinus syndrome.

8.22 Other TAVI-related complications

Table 9: Other TAVI-related complications

Conversion to open surgery
Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications
Unplanned use of cardiopulmonary bypass (CPB)
Unplanned use of CPB for haemodynamic support at any time during the TAVI procedure
Coronary obstruction
Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure
Ventricular septal perforation
Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure
Mitral valve apparatus damage or dysfunction
Angiographic or echocardiographic evidence of new damage (chordae papillary muscle, or to the leaflet) to the mitral valve apparatus or dysfunction (e.g. restrictions due to the THV) of the mitral valve during or after the TAVI procedure
Cardiac tamponade
Evidence of a new pericardial effusion associated with haemodynamic instability and clearly related to the TAVI procedure
Endocarditis
Any one of the following
Fulfilment of the Duke endocarditis criteria[a]
Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation
Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy
Valve thrombosis
Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis
Valve malpositioning
Valve migration
After initial correct positioning, the valve prosthesis moves upwards or downwards, within the aortic annulus from its initial position, with or without consequences
Valve embolization
The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus
Ectopic valve deployment
Permanent deployment of the valve prosthesis in a location other than the aortic root
TAV-in-TAV deployment
An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the index procedure

TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve.
[a]Durack *et al.* [72].

8.23 Quality of life

The quality of life will be assessed by 2 standardized and validated questionnaires:

- EuroQoL (EQ-5D)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)-12

More detailed and comprehensive questionnaires are known to exist, but the ones above represent the best compromise between reliability and feasibility in the context of the present investigator-led study.

9 STATISTICAL ANALYSIS PLAN

All statistical analyses will be performed by an independent Statistical Committee. The analysis will be performed on an intention-to-treat (ITT) set, defined as all intentionally randomized patients, by randomization treatment. Supportive per-protocol analyses will be performed on the primary and key secondary endpoints. Correction for multiple testing to account for type I error will be performed according to Holm, and Bretz graphical approaches[25].

A detailed statistical analysis plan will be completed before the end of the study. In summary, continuous variables will be tested for normal distribution with the Kolmogorov-Smirnov test and with visual estimate of the QQ plot. Normally distributed variables will be presented as mean±SD and compared using the t test and one-way ANOVA. Otherwise, the median [inter-quartile range], Mann-Whitney U and Kruskal-Wallis tests will be used. Categorical variables will be summarized in terms of absolute and relative frequencies (percentages) and compared using $\chi 2$ test. Statistical significance will be established at $\alpha=0.05$ level. Formal type-I error control will be ensured for the primary and the secondary endpoint by correction for multiple testing according to Holm, and Bretz graphical approaches. Kaplan-Meyer curves will be plotted to describe survival free from adverse events, and difference between groups will be test will log-rank test. Further analyses will be performed setting as landmark the timing of TAVI procedure. Any confounding factor will be tested by Cox regression models. Variables with a p-value <0.1 in univariate analysis will be entered in a multivariate analysis to identify independent predictors. When appropriate, 95% CI will be calculated.

In addition to the analysis of the first event, we will assess the primary composite outcome using the Finkelstein-Schoenfeld method, which is based on the principle that each patient in the clinical trial is compared with every other patient in a pairwise manner. The pairwise comparison proceeds in a hierarchical fashion, using all-cause mortality, followed by the frequency of hospital readmission when patients cannot be differentiated on the basis of mortality. This method gives a greater importance to all-cause mortality. We will apply the Finkelstein–Schoenfeld and the win ratio methods (Pocock et al, Eur Heart J 2012) to the patients stratified according to sex (male vs. female) and surgical risk (inoperable vs. other), yielding four stratification pools.

9.1 Determination of sample size

The occurrence of the primary endpoint will be computed from the randomization. Therefore, adverse events occurring between randomization and TAVI procedure will be considered. The primary endpoint is the 1-year occurrence of all-cause death and hospital readmission for cardiovascular cause. The estimated rate of the primary endpoint is around 30%, considering the characteristics of the study population and the inclusion of adverse events before TAVI [1-29]. Overall, 560 (187 control arm and 373 experimental arm)

patients are required to exclude a difference in favor of the control group of more than 10% (alpha=5% and ß=20%). Considering a 1% attrition rate final sample size is inflated to 566 patients.

10 ETHICAL AND REGULATORY STANDARDS

10.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the investigator abides by the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines (ICH-GCP) in the latest version, in the conduct, evaluation, and documentation of the study. A copy of these documents will be provided to each center. The study will be carried out according to local legal requirements and international regulations.

10.2 Informed Consent of the Patient

Patients who meet all inclusion criteria and none of the exclusion criteria are deemed eligible. Before being enrolled into the clinical study, the patient must provide written consent to participate in the study after the nature, scope and possible consequences of the clinical study have been explained both orally and in writing. Patients should be aware that they will be followed for the study whether they undergo invasive strategy as allocated or not. All patients who signed informed consent must be listed on the Screening Log.

10.3 Approval of the Study Protocol

Before the start of the study, the study protocol and the informed consent form used at the site and other appropriate documents must be submitted and approved by the local Ethics Committee or Institutional Review Board and the appropriate regulatory authorities according to local legal requirements. Documentation of Ethics Committee/IRB approvals will be required before sites are activated to randomize.

10.4 Maintenance of Records

The Investigator agrees to obtain a correctly completed informed consent form for each patient included in the study. The investigator will maintain a personal list of patient numbers and patient names to allow records to be found later. The Investigator must maintain all study records, patient files and other source data for the maximum period permitted by the hospital, institution, or private practice. However national regulations should be considered and the longest time allowed by these rules would be counted. For trials conducted in the European Community, the Investigator is required to arrange for the retention of patient identification codes for at least 15 years after the completion or discontinuation of the trial.

10.5 Confidentiality

All patient names will remain confidential. Patients will be identified throughout documentation and evaluation by the number assigned to them by the study. Patients will be assured that all findings will be

stored on the the computer and handled with the strictest confidence. The Investigator agrees to maintain the confidentiality of the study protocol.

11 ADMINISTRATIVE RULES

11.1 Curriculum vitae

An updated copy of the curriculum vitae for each Investigator and co-Investigator will be provided prior to the beginning of the study.

11.2 Confidentiality agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the Investigators (or any company acting on their behalf), inclusive of this protocol and the patient case report forms are the exclusive property of the Cardiovascular Department of the University of Ferrara. They may not be given or disclosed by the Investigator or by any person within his authority, either in part or in totality, to any unauthorized person without the prior written formal consent. It is specified that the submission of this protocol and other necessary documentation to the ERC or a like body (IRB, CCPPRB...) is expressly permitted, the Ethics Committee members having the same obligation of confidentiality. The Investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

11.3 Record retention in investigating center(s)

The Investigator must maintain all study records, patient files, and other source data for the maximum period of time permitted by the hospital, institution, or private practice. National regulations, however, should be considered and the longest time allowed by these rules would be counted. For trials conducted in the European Community, the Investigator is required to arrange for the retention of patient identification codes for at least 15 years after the completion or discontinuation of the trial.

12 OWNERSHIP OF DATA AND USE OF THE STUDY RESULTS

The Sponsor has ownership of all data and results collected during this study. The full publication rights of the study data reside solely with the Steering Committee.

13 PUBLICATIONS

All study presentations and/or publication of the results will be based on clean, checked and validated data in order to ensure the accuracy of the results. Publication of the main findings of this study will be made based on the contributions of individuals to the overall study. All the trial participants (investigators and committee members) make a prior delegation of responsibility for primary presentation and/or primary publication of the results to the Steering Committee.

14 STUDY ADMINISTRATIVE INFORMATION

14.1 ADDRESS LIST

14.1.1 Study Committees

A detailed list of the Study Committees and of the members is reported in the Appendix A

14.1.2 Sponsor

Azienda USL di Bologna

Azienda Ospedaliero Universitaria di Ferrara

Azienda USL-IRCCS di Reggio Emilia

14.1.3 Principal Investigator

Gianmarco Iannopollo

UOC di Cardiologia, Ospedale Maggiore

Largo Nigrisoli 2, Bologna, Italy

14.1.4 Study Chairs

Gianni Casella

UOC di Cardiologia, Ospedale Maggiore

Largo Nigrisoli 2, Bologna, Italy

Vincenzo Guiducci

UOC di Cardiologia, Arcispedale Santa Maria Nuova

Viale Risorgimento 80, Reggio Emilia, Italy

14.1.5 Academic Research Organization

Cardiology Unit, University Hospital of Ferrara

Via Aldo Moro 8, Cona (FE), Italy

14.2 INSURANCE

Subjects who participate in this study will be insured against study related injury according to local regulatory requirements. A copy of the certificate is filed in each investigator site file and in the trial master file.

14.3 FUNDING AND SUPPORT

The project was presented for the call of Ricerca Finalizzata 2021 and obtained the grant by Ministero della Salute (GR-2021-12374295). During the study, to achieve the scientific goal of the study and to allow the coverage of the costs, the Steering Committee can integrate the study budget with further fund raising from private and public companies. In particular, the potential economic resources derived from private companies will be allocated to cover the costs of the aortic prothesis for the participating centers. The potential achievements will be immediately communicated to Sponsor and Regulatory Agencies (including Ethic Committee). Study supporters have no role in the study design, conduct, and publication of the primary as well as any secondary manuscripts.

15 REFERENCES

1) Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011 Jun 9;364(23):2187-98. doi: 10.1056/NEJMoa1103510.
2) Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010 Oct 21;363(17):1597-607. doi: 10.1056/NEJMoa1008232.
3) Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016 Apr 28;374(17):1609-20. doi: 10.1056/NEJMoa1514616.
4) Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019 May 2;380(18):1695-1705. doi: 10.1056/NEJMoa1814052.
5) Reardon MJ, Kleiman NS, Adams DH, Yakubov SJ, Coselli JS, Deeb GM et al. Outcomes in the Randomized CoreValve US Pivotal High Risk Trial in Patients With a Society of Thoracic Surgeons Risk Score of 7% or Less. JAMA Cardiol. 2016 Nov 1;1(8):945-949. doi: 10.1001/jamacardio.2016.2257.
6) Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2017 Apr 6;376(14):1321-1331. doi: 10.1056/NEJMoa1700456.
7) Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019 May 2;380(18):1706-1715.
8) Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022 Feb 12;43(7):561-632
9) Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP et al. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57:253–69.
10) Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J. 2012 Oct;33(19):2403-18.
11) Eggebrecht H, Schmermund A, Kahlert P, Erbel R, Voigtländer T, Mehta RH. Emergent cardiac surgery during transcatheter aortic valve implantation (TAVI): a weighted meta-analysis of 9,251 patients from 46 studies. EuroIntervention. 2013;8:1072–80.

12) Hein R, Abdel-Wahab M, Sievert H, Kuck KH, Voehringer M, Hambrecht R, et al, German Transcatheter Aortic Valve Interventions Registry Investigators. Outcome of patients after emergency conversion from transcatheter aortic valve implantation to surgery. EuroIntervention. 2013;9:446–51.

13) Walther T, Hamm CW, Schuler G, Berkowitsch A, Kötting J, Mangner N, et al. Perioperative results and complications in 15,964 transcatheter aortic valve replacements: prospective data from the GARY registry. J Am Coll Cardiol. 2015;65:2173–80.

14) Arsalan M, Kim WK, Van Linden A, Liebetrau C, Pollock BD, Filardo G, et al. Predictors and outcome of conversion to cardiac surgery during transcatheter aortic valve implantation. Eur J Cardiothorac Surg. 2018;54:267–72.

15) Eggebrecht H, Vaquerizo B, Moris C, Bossone E, Lämmer J, Czerny M, et al, European Registry on Emergent Cardiac Surgery during TAVI (EuRECS-TAVI). Incidence and outcomes of emergent cardiac surgery during transfemoral transcatheter aortic valve implantation (TAVI): insights from the European Registry on Emergent Cardiac Surgery during TAVI (EuRECS-TAVI). Eur Heart J. 2018;39:676–84.

16) Pineda AM, Harrison JK, Kleiman NS, Rihal CS, Kodali SK, Kirtane AJ, et al. Incidence and outcomes of surgical bailout during TAVR: insights from the STS/ACC TVT registry. JACC Cardiovasc Interv. 2019;12:1751–64.

17) González Saldivar H, Vicent Alaminos L, Rodríguez-Pascual C, de la Morena G, Fernández-Golfín C, Amorós C, et al. Prognosis of patients with severe aortic stenosis after the decision to perform an intervention. Rev Esp Cardiol (Engl Ed). 2019;72:392–7.

18) Bainey KR, Natarajan MK, Mercuri M, Lai T, Teoh K, Chu V, et al. Treatment assignment of high-risk symptomatic severe aortic stenosis patients referred for transcatheter aortic valve implantation. Am J Cardiol. 2013;112:100–3.

19) Marques A, Cale R, Cruz I, Joao I, Pereira AR, Alegria S, et al. What is the risk of a pa- tient with severe aortic stenosis while waiting for aortic valve intervention? Eur Heart J. 2020;41:ehaa946.1978.

20) Elbaz-Greener G, Masih S, Fang J, Ko DT, Lauck SB, Webb JG, et al. Temporal trends and clinical consequences of wait times for transcatheter aortic valve replacement: a population-based study. Circulation. 2018;138:483–93.

21) G.Elbaz-Greener G, B.Yarranton B, F.Qiu F, D.A.Wood DA, J.G.Webb JG, S.E.Fremes SE. Association between wait time for transcatheter aortic valve replacement and early postprocedural outcomes. J Am Heart Assoc. 2019;8:e010407.

22) EggebrechtH, MehtaRH, HaudeM, SackS, MudraH, HeinR,et al.Transcatheteraortic valve implantation (TAVI) by centres with and without an onsite cardiac surgery pro- gramme: preliminary experience from the German TAVI registry. Eurointervention. 2014;10:602–8.

23) Gafoor S, Sirotina M, Doss M, Franke J, Piayda K, Lam S, et al. Safety of transcatheter aortic valve implantation in a hospital with visiting on-site cardiac surgery. J Interv Cardiol. 2015;28:76–81.

24) Eggebrecht H, Bestehorn M, Haude M, Schmermund A, Bestehorn K, Voigtländer T, et al. Outcomes of transfemoral transcatheter aortic valve implantation at hospitals with and without on-site cardiac surgery department: insights from the prospective German aortic valve replacement quality assurance registry (AQUA) in 17919 patients. Eur Heart J. 2016;37:22408.

25) EggerF, ZweikerD, FreynhoferMK, LöfflerV, Rohla M, Geppert A,et al, AustrianTAVI Group. Impact of on-site cardiac surgery on clinical outcomes after transfemoral transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2018;11:2160–7.

26) Roa Garrido J, Jimenez Mazuecos J, Sigismondi A, Cardenal-Piris R, Gallardo-López A, Vaquerizo B, et al. Transfemoral TAVR at hospitals without on-site Cardiac Surgery Department in Spain: a multicenter registry. JACC Cardiovasc Interv. 2019;12:896–8.

27) Arnold SV, Reynolds MR, Lei Y, Magnuson EA, Kirtane AJ, Kodali SK et al. Predictors of poor outcomes after transcatheter aortic valve re- placement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. Circulation 2014;129:2682–2690.

28) Lung B, Laouenan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P et al. Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. Heart 2014; 100:1016–1023.

29) Puls M, Sobisiak B, Bleckmann A, Jacobshagen C, Danner BC, Hunlich M et al. Impact of frailty on short- and long-term morbidity and mortality after transcatheter aortic valve implantation: risk assessment by Katz Index of activities of daily living. EuroIntervention 2014;10:609–619.

30) Genereux P, Piazza N, Alu M, Nazif T, Hahn R, Pibarot P, et al. Valve Academic research Consortium 3: Updated endpoint definitions for Aortic Valve Clinical research. J Am Coll Cardiol 2021 Jun;77(21):2717-46.