Transcatheter aortic-valve implantation with or without on-site cardiac surgery: The TRACS trial

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ABSTRACT

Background Transcatheter aortic valve implantation (TAVI) has emerged as an effective and safe treatment for patients with symptomatic aortic stenosis. The indication to TAVI should be agreed upon by a Heart Team, and the procedure should be performed in centers with on-site cardiac surgery. However, TAVI complications requiring emergent cardiac surgery (ECS) have become very rare. Concurrently, access disparities and prolonged waiting times are pressing issues due to increasing clinical demand of TAVI. Many solutions have been proposed and one of them is the possibility of performing TAVI in centers without on-site cardiac surgery.

Methods and Design The Transcatheter Aortic-Valve Implantation with or without on-site Cardiac Surgery (TRACS) trial is a prospective, randomized, multicenter, open-label study with blinded adjudicated evaluation of outcomes. Patients with symptomatic severe aortic stenosis and deemed inoperable, at high surgical risk, or presenting with at least 1 clinical factor compromising the benefit/risk ratio for ECS, will be randomized to undergo TAVI either in centers with or without on-site cardiac surgery. The primary endpoint will be the composite occurrence of all-cause death, stroke, and hospital readmission for cardiovascular causes at one year. The safety endpoint will include death attributable to periprocedural complications actionable by ECS. The study aims to enroll 566 patients.

Implications The TRACS trial aims to address critical gaps in knowledge regarding the safety and efficacy of TAVI procedures performed in centers without on-site cardiac surgery, potentially improving access and outcomes for high-risk patients.

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Background

Transcatheter aortic valve implantation (TAVI) is a treatment option for individuals with symptomatic severe aortic stenosis (AS). Landmark trials have established robust evidence supporting the safety, feasibility, and efficacy of TAVI, employing both self-expanding and balloon-expanding prostheses.[1-7] These studies included patients across a spectrum of different surgical risk for aortic valve replacement, ranging from low to prohibitive, which has contributed to the global acceptance of TAVI in clinical practice.[1-7] International guidelines have endorsed TAVI as a suitable option, with decisions made

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collaboratively by a specialized Heart Team (HT).[8] Over the last decade, there has been a notable rise in the worldwide utilization of TAVI, resulting in favorable effects on mortality rates among AS patients.[9] Despite these advancements, recent large-scale registry data indicate persistently low rates of aortic valve replacement for severe AS patients, with only 60% receiving treatment up to 4 years after their initial diagnosis.[10] Furthermore, the risk of mortality in AS patients increases incrementally across the entire spectrum of AS severity, underscoring the necessity of earlier interventions.[10] Geographically and demographically, there is substantial variability in the utilization of TAVI, which may contribute to variations in mortality rates associated with AS.[9] The "Valve for Life" initiative by the European Association of Percutaneous Cardiovascular Intervention (EAPCI) has shown significantly lower TAVI procedure numbers in the UK compared to other European countries, with notable geographic disparities in access to TAVI within the UK.[11] The limited access has resulted in prolonged waiting times for TAVI (averaging 141 days), resulting in significant mortality among those awaiting intervention. This prolonged wait has been associated with clinical deterioration and acute hospital admissions, as well as death, which could potentially be avoided.[11] Previous registry data emphasize that extended wait times for TAVI are linked to higher mortality rates, increased hospitalization for heart failure, and the necessity of urgent procedures. In Ontario, Canada, during the initial phase of TAVI therapy development, patients awaiting the procedure faced mortality rates ranging from 10% to 14%.[12] From 2010 to 2016, the cumulative probability of TAVI wait list mortality in a predominantly inoperable and high-risk population was 4.3%. Recent reports from Canada show a cumulative probability of wait-list mortality and heart failure hospitalization at 80 days, standing at around 2% and 12%, respectively, with a consistent rise in events with increasing waiting times.[13] Interestingly, despite a year-over-year increase in overall TAVI procedure capacity at sites with on-site cardiac surgery capabilities, median wait times increased across all provinces over time (from 107 days in 2014-2015 to 135 days in 2016-2017), with significant variation between provinces, ranging from 71.5 days in Newfoundland to 190.5 and 203 days in Manitoba and Alberta, respectively.[14] Despite efforts to enhance the efficiency of existing sites through streamlined care pathways and minimalistic TAVI approaches to reduce hospitalization duration,[15] as a consequence of the growing indications as suggested by guidelines, the demand for TAVI procedures has outpaced the growth in capacity at centers with on-site cardiac surgery.

The role of the heart team

The HT consists of a proficient group of healthcare professionals, including clinical and interventional cardiologists, cardiac surgeons, interventional imaging specialists, cardiovascular anesthesiologists, and, when necessary, other specialists such as heart failure specialists, electrophysiologists, or geriatricians. The role of the HT is paramount as it enables a comprehensive discussion on the accuracy of surgical risk scores, considers additional factors like unaccounted comorbidities or frailty, and conducts a risk-benefit analysis that encompasses variables not always captured in standard procedures or protocols. Therefore, the HT plays a crucial part in decision-making, and its consultation for the treatment of valvular heart disease is strongly endorsed by scientific societies.[8] The importance of the HT is not limited to the evaluation and selection of candidates for TAVI, but it is also crucial to estimate the risk-benefit of the procedure as well as the risk of potential complications associated with TAVI.

TAVI procedure

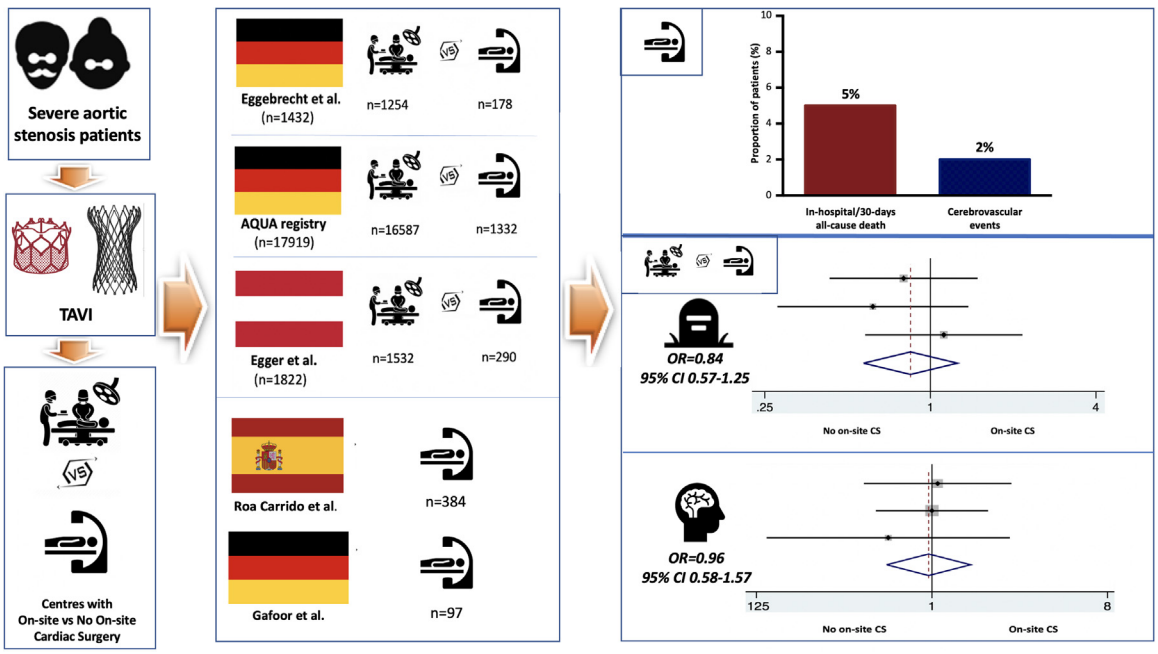
TAVI interventions exhibit significant learning curve features, showing enhanced procedural safety and reduced mortality rates when conducted by expert operators.[16] Despite refinements in the technique, various complications may arise during the TAVI procedure. The incidence of post-TAVI complications varies considerably across studies and could be limited by the experience of the operators.[17-34] The majority of complications arise from issues related to vascular access, bleeding, and the requirement of a pacemaker. Procedural complications that may benefit from immediate cardiac surgery (ECS) include valve migration or embolization, ventricular perforation, coronary obstruction, mitral valve damage, annular rupture, and aortic dissection. Complications requiring ECS have decreased over time and have become extremely uncommon among different groups of patients.[35,36] A recent nationwide study in the US has documented that less than 0.5% of TAVI procedures resulted in complications necessitating ECS.[37] Data from the Leipzig Heart Centre registry indicates a progressive decline in TAVI procedural complications necessitating ECS over the past decade (3.5% in 2006-2010, 1.4% in 2011-2015, and 0.4% in 2016-2020), reaching a rarity of less than 0.5%.[38] In addition, these complications requiring immediate ECS are linked to unfavorable outcomes, with an overall 1-year survival rate of 37.8%, even worse in high-risk patients (in-hospital and 1-year survival rates following ECS were 37.9% and 31.8%, respectively) who comprise all the intraprocedural deaths.[38] In the case of low-intermediate risk patients, most complications are potentially eligible for surgical correction, with a 1-year survival as high as 87%.[38] It is noteworthy that the number needed to treat for high-risk TAVI patients undergoing ECS was 625, suggesting that 1 ECS procedure would have saved one life for every 156.250 TAVI procedures in this particular population.[38] Various factors may have contributed to the enhanced safety of the procedure over the past decade. Careful preprocedural planning, incor-

porating routine CT scan imaging for refining procedural strategies, along with HT evaluation, has been crucial in anticipating potential severe complications. This approach facilitates proper patient selection and optimal selection of valve type and size. Additionally, advancements in procedural aspects, such as echo-guided femoral artery puncture, single femoral arterial access, local instead of general anesthesia, and left ventricular pacing with the working wire instead of separate transvenous pacing, have played a role. Technical improvements in valves, such as reduced sheath size, enhanced coronary access, and improved transcatheter valve systems, have undeniably contributed to making the TAVI procedure more feasible and safer.[39–41] Despite the decreasing incidence of ECS, international guidelines maintain a Class I recommendation, albeit with Level C evidence, that TAVI procedures should ideally be performed at centers equipped with on-site cardiac surgery. This recommendation underscores the consensus that the presence of a HT and experienced TAVI operators within such centers ensures optimal patient outcomes.

TAVI procedure in centers without on-site cardiac surgery

Initial experiences with TAVI procedures conducted in centers without on-site cardiac surgery, as indicated by observational studies, demonstrate favourable procedural and clinical outcomes (Figure 1).[42–46] In 2014, Eggebrecht et al.[42] conducted the first study investigating the outcomes of severe symptomatic AS patients undergoing TAVI at hospitals without on-site cardiac surgery. They compared 1254 patients treated at 27 German hospitals with on-site surgery and 178 patients treated at 8 hospitals without this facility, all implanted between 2009 and 2010 with first-generation valves. Results showed no significant differences in major complications or 30-day mortality rates between the groups. Gafoor et al.[43] reported on 97 high-risk AS patients treated with TAVI at a single center in Frankfurt with a visiting surgical team, achieving 100% technical success. The AQUA registry, mandatory for German inpatient procedures, analysed 17919 TAVI patients in 2016. Patients in hospitals without on-site surgery were older with higher predicted risks but showed similar in-hospital mortality and conversion to surgery rates compared to those treated in hospitals with on-site surgery.[43,44] Egger et al.[45] analyzed data from the Austrian TAVI registry, finding no significant differences in mortality rates between patients treated in institutions with and without on-site cardiac surgery after propensity matching. Additionally, a Spanish study assessed TAVI safety in centres without on-site surgery but with a nearby cardiac surgery centre. The study included

Figure 1. Overview of studies on TAVI procedures carried out in centers without onsite cardiac surgery. TAVI, Transcatheter aortic valve implantation. Panel A (upper right) shows pooled estimates of short-term mortality and cerebrovascular event rates from five studies depicted in the figure, focusing on patients undergoing TAVI in centers without on-site cardiac surgery (CS)., Panel B (lower right) shows a meta-analysis comparing TAVI outcomes with and without on-site cardiac CS. Data from matched populations were utilized for the analysis. Risk is illustrated as odds ratios and 95% confidence intervals for short-term mortality and cerebrovascular events.



384 patients, showing high technical success rates and relatively low mortality rates, indicating the feasibility and safety of TAVI in such settings.[46] Data from Austrian, German, and Spanish registries reveal that despite patients undergoing TAVI in hospitals without on-site cardiac surgery have a higher-risk profile, adjustments for potential confounders show comparable short- and long-term mortality rates to those treated with on-site cardiac surgery (Figure 1).[42-46] Panel A of the Figure 1 reports the pooled estimates of short-term mortality and cerebrovascular event rates from the 5 studies focusing on the group of patients undergoing TAVI in centers without on-site cardiac surgery (CS),[42-46] with rates respectively at 5% and 2% (Figure 1).[47] Panel B of the Figure 1 shows a meta-analysis of matched populations from studies comparing TAVI outcomes between centers with and without CS.[42,44,45] Short-term mortality (OR = 0.84, 95%CI, 0.57-1.25) and cerebrovascular events (OR = 0.96, 95%CI, 0.58-1.57) showed no significant difference among patients undergoing TAVI at centers with or without on-site CS.

Rationale for performing TAVI in centers without on-site cardiac surgery

Initial assessments from centers conducting TAVI without on-site cardiac surgery have indicated positive clinical and safety outcomes.[42-46] However, the retrospective and not randomized nature of these studies, with inherent limitations, fails to provide sufficiently robust evidence to advocate for the expansion of TAVI to facilities lacking on-site cardiac surgery. Several justifications support performing TAVI in centers without on-site cardiac surgery. Firstly, common complications such as bleeding, access site-related issues, and pacemaker implantation can be effectively managed in these centers. Secondly, instances requiring ECS are rare (<0.5%), and despite surgical intervention, the mortality remains significant, particularly in patients with a high surgical risk profile. Thirdly, a median waiting time for TAVI of approximately 3 months is associated with a risk of mortality and hospitalization for heart failure of around 4% and 15%, respectively. The likelihood of death or hospitalization steadily increases with prolonged waiting times, without a discernible threshold where event rates plateau. Allowing treatment of inoperable or high surgical risk patients in centers without on-site cardiac surgery could significantly reduce TAVI waiting times, even in centers with on-site cardiac surgery, thereby mitigating the occurrence of fatal adverse events while awaiting treatment. Additionally, this approach could potentially free up more hospital beds and cath-lab schedules at hub centers, facilitating streamlined treatment pathways for patients with low cardiovascular surgery risk or those requiring complex TAVI or other structural interventions. The hypothesis of the TRanscatheter Aortic-Valve Implantation with or without on-site Cardiac Surgery (TRACS) trial is that minimizing periprocedural complications with careful selection of patients by an experienced HT, meticulously planning the procedure and executing it by proficient operators could reduce the TAVI pathway associated clinical risks. Therefore, TRACS investigators hypothesize that a TAVI pathway involving experienced operators performing the procedure in a center without on-site cardiac surgery is non-inferior to the conventional scenario where the same team conducts the procedure in a center with on-site cardiac surgery.

Methods

Study design and population

The TRanscatheter Aortic-Valve Implantation with or without on-site Cardiac Surgery (TRACS) trial is an all-comer, prospective, randomized, multicenter, open-label study with blinded adjudicated evaluation of outcomes (PROBE). The study flow chart is reported in Figure 2. The sponsor of the study are the Italian healthcare organizations Azienda USL di Bologna, Azienda Ospedaliero-Universitaria di Ferrara and Azienda USL-IRCCS Reggio Emilia (Emilia-Romagna region, Italy). The protocol has received approval from the institutional review boards in all participating centers. Patients will be included if they meet all the following inclusion criteria (Table 1): (1) symptomatic severe AS; (2) indication to TAVI confirmed by the multidisciplinary HT; and (3) one of the subsequent characteristics by unanimous judgment of the HT: (1) prohibitive surgical risk, (2) high surgical risk (STS PROM >8%), (3) the presence of at least 1 clinical factors that compromises the benefit/risk ratio in the case of ECS. The list of factors compromising the benefit/risk ratio in the case of ECS is detailed in Table 1. The main exclusion criteria are: (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.

Study procedures

Participating centers

The TRACS trial involves centers classified as 'centers without on-site cardiac surgery.' These centers are responsible for patient selection and enrollment. A comprehensive set of restrictive criteria outlining the qualifications for a center to be considered as a participant is outlined in Table 2. Each participating center is responsible for designating the "study HT" and the "study TAVI operators". In particular, participating centers are required to have established standard operating procedures of collaboration with external cardiac surgery departments, which include weekly structured discussions of the Heart Team that involve affiliated cardiac surgeons. Table 2 provides a detailed account of the criteria for designating an individual as a study TAVI operator. Specifically, the designated study TAVI operators are interven-

Figure 2. Study flow chart. CV, cardiovascular; TAVI, Transcatheter Aortic Valve Implantation; ECS, emergent cardiac surgery.

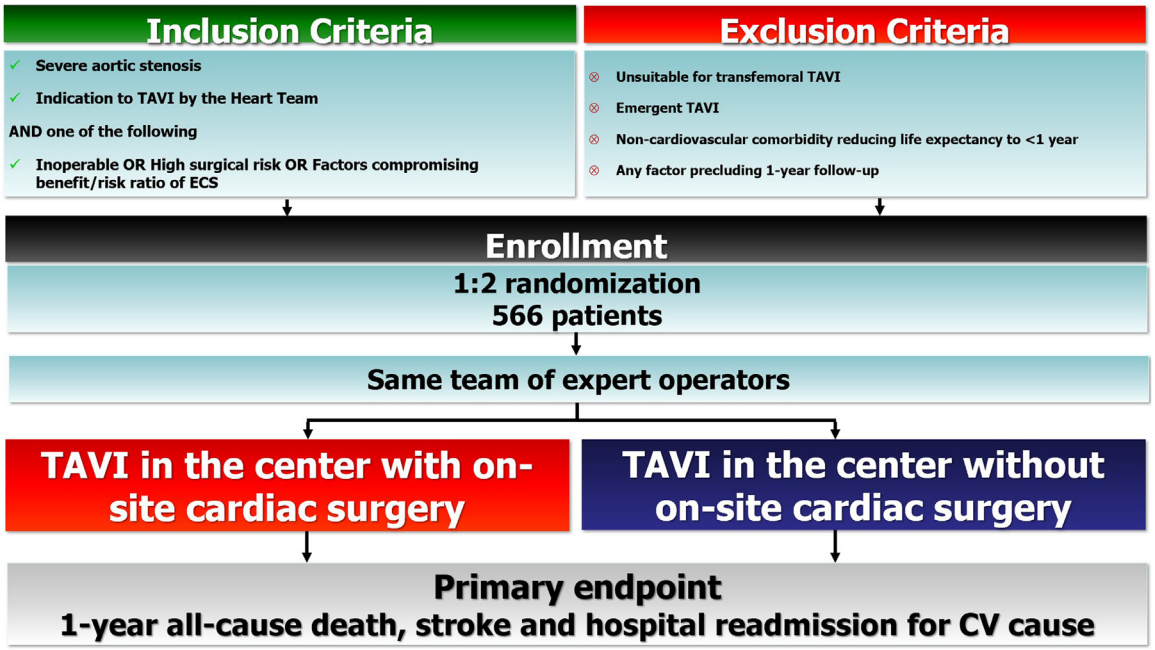


Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion
Symptomatic severe aortic stenosis Indication to TAVI *and one of the following* 1. Inoperable due to prohibitive surgical risk 2. High surgical risk (STS score >8%) 3. At least one factor compromising the benefit/risk of ECS Porcelain aorta or severely atherosclerotic aorta Frailty/Reduced physical performance Cognitive impairment, dementia, or Parkinson's disease Severe liver disease/cirrhosis Hostile chest IMA or other 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	Unsuitable for transfemoral TAVI Emergent TAVI Noncardiovascular comorbidity reducing life expectancy to <1 year Any factor precluding 1-year follow-up Refusal of informed consent

ECS, emergent cardiac surgery; IMA: internal mammary artery; STS: Society of Thoracic Surgery; TAVI: transcatheter aortic valve replacement.

tional cardiologists (or cardiac surgeon) who have a minimum of two years of TAVI experience and have successfully completed at least 50 TAVI procedures as primary operators at centers with on-site cardiac surgery. Operators or teams will work in the same modality in both arms, they can be operators of the centers with or without on-site CS and the same operators will be operative in both centers with or without on-site CS.

Patient screening

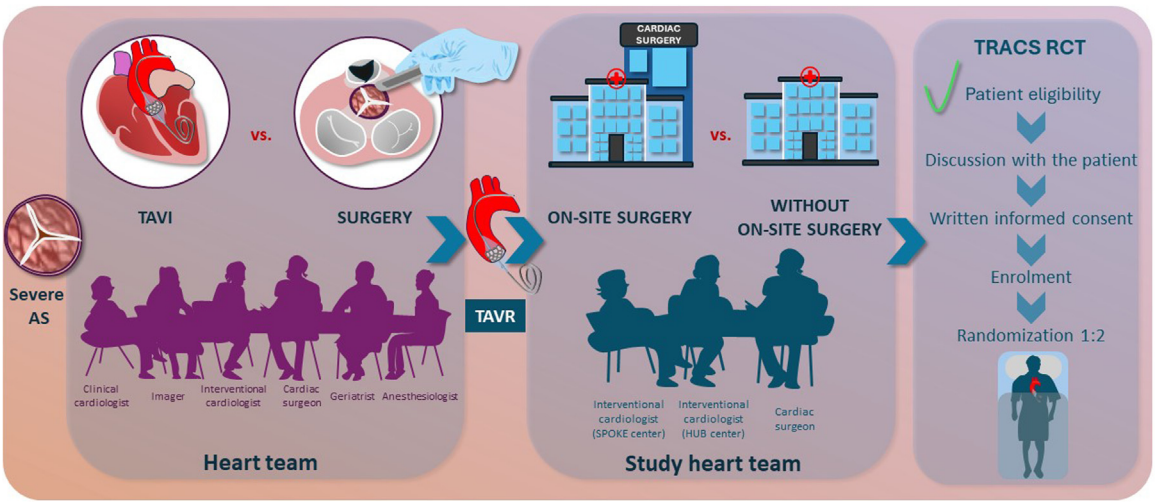
Following the completion of all necessary examinations (including transthoracic echocardiography, clinical history, laboratory tests, coronary artery angiography, and computed tomography for aortic assessment and vascular access), the "multidisciplinary HT" will reach a consensus on the TAVI indication (Figure 3). The multidisciplinary HT refers to the standard HT used in routine clin-

Table 2. Requirements for participating centers and TAVI operators

Participating centers	TAVI operators
Availability of a standard operating procedure with an external cardiac surgery department to ensure an established, weekly Heart Team discussion that includes participation from affiliated cardiac surgeons.	At least 5-year experience in coronary interventions
Availability of standard operating procedure for rapid transfer of patients with procedural complications to cardiac surgery with a maximum delay of 60 minutes	More than 75 PCIs by year
Five-year experience in screening, selection, and management of TAVI patients	Experience in the use of tools for the retrieval of intravascular foreign bodies
At least 2 certified operators or a dedicated intercenter team performing TAVI procedure	Experience in pericardiocentesis
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.	Experience with ultrasound-guided puncture of the femoral artery
At least 5-year experience in advanced cardiac imaging including transesophageal echocardiography and cardiac computed tomography	Experience in suture-mediated closure of femoral artery access and in the management of large bore sheaths
On-site vascular surgery or on-site availability of certified surgeon and operating room allowing the surgical treatment of vascular complications	Experience in the management of peripheral vascular complications
On-site electrophysiology laboratory (permanent pacemaker implantation)	At least 2 years of experience in TAVI procedures as first and second operator at centers with on-site cardiac surgery
On-site Level 2 Intensive Cardiac Care Unit	At least 50 TAVI procedures as first operator at centers with on-site cardiac surgery
	More than 20 TAVI procedures per year at centers with on-site cardiac surgery

TAVI, transcatheter aortic valve replacement.

Figure 3. Role of the heart team and patient journey from indication to randomization. AS, aortic stenosis; TAVI, transcatheter aortic valve implantation; TRACS, TRanscatheter Aortic-Valve Implantation with or without on-site Cardiac Surgery; RCT, randomized clinical trial.



ical practice, which comprises specialists such as clinical and interventional cardiologists, cardiac surgeons, interventional imaging specialists, cardiovascular anesthesiologists, and, when necessary, other specialists such as heart failure specialists, electrophysiologists, or geriatricians. This HT is on charge to indicate TAVI vs aortic valve replacement vs medical therapy (futility of intervention). Subsequently, the study HT will evaluate eligibility for the study, a decision that requires unanimous agreement from all members of the Study HT (Figure 3). The study HT refers specifically to the team convened for this trial, which includes an interventional cardiologist from the center without cardiac surgery (SPOKE center), an interventional cardiologist from the center with

cardiac surgery on-site (HUB center), and a cardiac surgeon (Figure 3). Upon confirmation, discussions about the study will be held with the patient and their relatives. The study investigator will engage in conversations about the study's design and procedures, elucidating its strengths and limitations (Figure 3). Detailed information about the potential risks associated with study participation and alternative options will be provided. Only after a thorough discussion, the patient will sign the informed consent. Randomization of patients is allowed only following the completion of the informed consent process. Data will be recorded in electronic case report forms (eCRF) (https://redcap.ospfe.it), with the quality of the data subject to review by the Academic Research Organization (ARO) at the University Hospital of Ferrara.

Randomization and treatment protocol

Centralized randomization through an internet-based system will assign both the patient identification number (Patient ID) and treatment allocation. The allocation will follow a computer-generated randomization list, stratified by center, sex, surgical risk (inoperable vs other), age (<85 vs ≥85 years), and valve type (self-expandable vs balloon-expandable). Patients will be randomized into either the experimental arm (TAVI without on-site cardiac surgery) or the control arm (TAVI with on-site cardiac surgery) with a 2:1 ratio. Patients randomized to the experimental arm will receive TAVI procedure in the hospital without on-site surgery. Conversely, patients randomized to control arm will receive the TAVI procedure in the referring center with on-site surgery. The team of TAVI operators performing TAVI procedures is the same in both study arms. All randomized patients, regardless of subsequent eligibility confirmation or actual treatment allocation, are irrevocably included in the study.

General information regarding TAVI procedure

The TAVI procedure will adhere to existing guidelines and institutional protocols, with the designated study TAVI operators responsible for its execution. They will have discretion over decisions regarding site access management, valve type, and size. Post-TAVI procedure monitoring, as well as subsequent patient mobilization and management, will follow prevailing guidelines and institutional standards.

Follow-up visits

After hospital discharge, patients will have routine clinic follow-ups at 1, 6, 12 months, and annually up to 3 years. These visits will assess clinical outcomes, compliance with medical therapy, and quality of life (EQ-5D).

Study endpoints

The primary efficacy endpoint is the 1-year cumulative occurrence of all-cause death, stroke, and hospital readmission for cardiovascular (CV) causes. The primary endpoint of the study was selected in agreement with the suggestions of the consensus documents of the VARC-3.[48] This endpoint aims to evaluate whether a TAVI pathway led by experienced operators without on-site cardiac surgery is non-inferior compared to a pathway with the same team performing the procedure in a center with on-site cardiac surgery. Hospitalization for cardiovascular causes includes any nonelective hospital admission due to cardiovascular cause (eg myocardial infarction, heart failure, arrhythmias, urgent or unscheduled cardiological procedures, etc.) postrandomization until the end of follow-up. Adverse events will be collected from randomization, covering those occurring before, during and after the TAVI procedure. The primary safety endpoint is death due to periprocedural complications actionable by ECS, defined as cardiothoracic surgical intervention with cardiopulmonary bypass for urgent complications requiring aortic valve replacement, repair of myocardial or aortic injury, or pericardial drainage within 72 hours after TAVI. A detailed list of secondary and other safety endpoints is available in Table 3. An independent Clini-

Table 3. Efficacy and safety endpoints

Efficacy	Safety
Primary	*Primary*
All-cause death, stroke and hospital readmission for CV cause	Death due periprocedural complications actionable by ECS
Secondary	*Secondary*
All-cause death	Cardiac tamponade
Cardiovascular death	Bleeding
Myocardial infarction	Kidney failure (requirement for renal replacement therapy)
Hospital admission for cardiovascular cause	Severe aortic regurgitation
Hospital admission for heart failure	Multiorgan failure (failure of at least two organ systems)
Cerebrovascular accident	Vascular access site and access related complications
Ischemic stroke	Conduction disturbances and arrhythmias
Hospital admission for pneumonia (± respiratory failure)	Endocarditis
Need for balloon aortic valvuloplasty for emergent condition	Valve thrombosis
Quality of life measured with the Eq-5D and KCCQ-12 scales	Valve malpositioning
Time spent on the waiting list	Valve embolization
	Ectopic valve deployment
	TAV-in-TAV deployment

CV, cardiovascular; KCCQ, Kansas City Cardiomyopathy Questionnaire; ECS, emergent cardiac surgery; TAV, transaortic valve.

cal Event Committee (CEC) will adjudicate all endpoints. The CEC members and management team will be blinded to randomization and patient identifying information, adjudicating events based on the VARC-3 consensus document.[48]

Statistical considerations

All statistical analyses will be performed by an independent Statistical Committee on an intention-to-treat (ITT) basis, comprising all patients intentionally randomized according to treatment assignment. Supportive per-protocol analyses will be conducted on the primary and key secondary endpoints. A detailed statistical analysis plan will be completed before the end of the study.

In summary, continuous variables will be assessed 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 1-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 tested with 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.

Determination of sample size

The sample size calculation will account for the occurrence of the primary endpoint from randomization, including adverse events occurring up to the TAVI procedure. The estimated rate of the primary endpoint is approximately 30%, taking into account the study population characteristics and pre-TAVI adverse events.[1-29] To exclude a difference in favor of the control group greater than 10%, with a significance level (alpha) of 5% and power (beta) of 80%, a total of 560 patients are required. Factoring in a 1% attrition rate, the final sample size is adjusted to 566 patients, with 189 in the control arm and 377 in the experimental arm.

Study organization

The TRACS trial is currently underway in Italy, and any additional sites joining the trial will be documented on the website's dedicated section (https://elementrials.org/aqva). The Executive Committee leading the study consists of Gianmarco Iannopollo (Principal Investigator), Gianni Casella (Study Chair), and Vincenzo Guiducci (Study Chair). The data safety monitoring board (DSMB) includes a mix of general cardiologists, interventional cardiologists and cardiac surgeons. The statistical analysis will be conducted by an independent team of statisticians (We4 Clinical Research, https://we4cr.com).

State of the art, timelines, and conclusions

The study was registered on March 2nd, 2023, with the ClinicalTrials.gov Identifier NCT05751577. The approval of the Ethics Committee of the coordinating center (Comitato Etico Area Vasta Emilia Centro) was obtained in January 2023. The enrollment phase started on May 2023, with most of the 11 active centers starting their enrolment phase in the last quarter of 2024. By October 2024, a total of 200 patients have been enrolled. By the end of 2024, at least other 3-5 centers will be activated. The timeline for the end of the enrollment is scheduled for December 2025. The primary endpoint of the last patient will be available in December 2026. The follow-up will continue for up to 3 years.

Discussion

Based on international guidelines, TAVI procedures must be performed in centers with on-site cardiac surgery.[8] Advancements in device technology, procedural techniques, CT imaging analysis, and operator experience have collectively reduced the incidence of TAVI-related complications necessitating ECS. Despite these improvements, studies have consistently shown high mortality rates associated with complications requiring ECS, particularly in high-risk patient groups. Preliminary observational studies suggest that performing TAVI procedures in centers without on-site cardiac surgery may be feasible. This hypothesis, however, must be confirmed by randomized clinical trials. Such a shift could potentially enhance procedural availability, reduce waiting times, and mitigate adverse events during the preprocedural period. The TRACS trial represents the first randomized study specifically designed to evaluate the efficacy and safety of TAVI in centers lacking on-site cardiac surgery facilities. This trial is crucial in assessing whether TAVI pathways in such centers can achieve outcomes that are noninferior to those seen in centers with on-site surgical capabilities. While this recommendation is classified as Class I and supported by Level C evidence based on expert opinion, there is a lack of randomized trials clearly demonstrating the efficacy of this practice. Consequently, the TRACS trial will systematically and scientifically evaluate the validity of current recommendations and common clinical approaches, particularly focusing on inoperable or high surgical risk patients undergoing TAVI. Its primary objective is to evaluate whether TAVI pathways in centers without on-site cardiac surgery can maintain noninferiority compared to those in centers with such facilities. According to the

TRACS trial, TAVI without on-site cardiac surgery represents an "expanded" platform where experienced operators may treat selected patients after extensive discussion with the HT in suitable centers without on-site cardiac surgery. The network with the Heart Valve Center will remain essential for sharing training, determining procedure indications, managing TAVI patients, and facilitating a unified waiting list.

Study limitations

The TRACS trial acknowledges some limitations. Firstly, it is focused on patients who are either deemed inoperable, high-risk candidates, or exhibit at least one clinical factor that jeopardizes the benefit-to-risk ratio of ECS. The results will not be transferable to low-intermediate surgical risk subjects. Secondly, the trial is open-label, which precludes blinding of the operator and patient to the hospital where the TAVI intervention occurs. However, strategies such as intention-to-treat analysis and objective endpoint adjudication by an independent Clinical Event Committee (CEC) will mitigate potential bias. Thirdly, the sample size calculation is based on the occurrence of the primary efficacy endpoint, which may limit power to detect differences in the primary safety endpoint. The events included in the primary safety endpoint are extremely rare (less than 0.4% of TAVI procedures),[38] giving the rationale for the present study. Consequently, the primary safety endpoint was not powered, as it would require enrolling a significant number of patients to identify even a small difference in such a rare event.

Conflict of interest

Gianmarco Iannopollo received funding from the Italian Health Minister (Ricerca Finalizzata 2021, GR-2021-12374295) for the conduction of studies on TAVI in patients with severe aortic stenosis. Gianluca Campo: research grants from SMT, Medis, Eukon, Siemens, Astrazeneca, Guerbet, Boston Scientific, Amgen; speaking or consulting fees from Astrazeneca, Menarini, Abbott, Boston Scientific.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2024.10.019.

CRediT authorship contribution statement

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