IRON-TAVI

Exercise and Diet Supplements for Older Patients undergoing TAVI: the IRON-TAVI trial

Version number 1, May 11, 2026

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: Elisabetta Tonet

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

SUMMARY

1 BACKGROUND

Severe aortic stenosis (AS) is one of the most common valvular diseases in older adults and its prevalence is expected to rise further with population ageing. Once symptoms occur, the natural history of untreated severe AS is characterized by rapid clinical deterioration, recurrent hospitalization, and excess mortality. Over the last decade, transcatheter aortic valve implantation (TAVI) has transformed the treatment of symptomatic severe AS and, according to contemporary European recommendations, has become the preferred treatment strategy for most anatomically suitable older patients, with Heart Team discussion remaining central to treatment selection and timing [1]. The expansion of TAVI has been one of the major success stories of modern structural cardiology. Progressive refinement of devices, vascular access techniques, procedural imaging, periprocedural management, and operator experience has led to very high procedural success rates and lower rates of catastrophic complications. As a consequence, the clinical discussion has progressively moved beyond the technical feasibility of the procedure itself toward a more complex question: which patients will derive a meaningful benefit from TAVI in terms not only of survival, but also of symptoms, physical function, autonomy, and quality of life? This issue is particularly relevant in the oldest and frailest segment of the TAVI population, in whom severe AS coexists with sarcopenia, multimorbidity, disability, and nutritional impairment. This distinction between procedural success and patient-centred success is clinically crucial. A technically successful valve procedure does not automatically translate into recovery of mobility, functional independence, or durable improvement in health status. Contemporary observational studies have consistently shown that a substantial proportion of patients undergoing TAVI continue to experience poor health status, limited symptomatic improvement, recurrent heart failure hospitalization, or early mortality despite apparently successful valve replacement [2,3]. In other words, TAVI may correct the valvular lesion while failing to reverse the global biological vulnerability of the older patient. This concept is tightly linked to the broader issue of futility in TAVI. The concept of futility in TAVI has evolved from a narrow, mortality-based definition toward a broader patient-centred framework. In contemporary practice, futility should not be understood simply as death after the procedure, but rather as failure to achieve a clinically meaningful improvement in survival, symptoms, physical function, or quality of life that is aligned with the goals of care of the individual patient. Several reports and reviews have emphasized that prolonged survival without improvement in autonomy or symptom burden may be of limited value in very old and frail patients [4,5]. This is precisely the population in which better pre-procedural phenotyping and targeted peri-procedural interventions are most needed. Among the determinants of incomplete recovery after TAVI, frailty has consistently emerged as one of the strongest. Frailty is a multidimensional syndrome characterized by reduced physiologic reserve and impaired resilience to stressors. However, in the TAVI setting, frailty should not be considered an abstract geriatric label. Its most clinically

relevant and actionable components are often reduced physical performance, malnutrition, and sarcopenia. These domains are highly prevalent in patients referred for TAVI and are strongly interrelated. Severe AS promotes fatigue, exertional dyspnoea, reduced mobility, and progressive deconditioning. Reduced physical activity leads in turn to loss of muscle mass and muscle quality, which worsens gait speed, balance, and lower-extremity strength. At the same time, anorexia of ageing, chronic inflammation, comorbidity burden, polypharmacy, and recurrent episodes of congestion or hospitalization may impair nutritional intake and accelerate catabolism. The result is a vicious circle in which malnutrition, frailty, and sarcopenia reinforce each other and predispose to poor recovery even after the obstructive lesion has been treated. This pathophysiological continuum is particularly relevant in severe AS. Older patients with severe AS often reduce their daily activity long before the procedure because of dyspnoea, exertional intolerance, fear of syncope, and global fatigue. The consequent decline in mobility and muscle conditioning is not simply a marker of disease severity; it also becomes an independent determinant of outcome. Likewise, poor nutritional status is not only a bystander reflecting comorbidity burden, but a biological substrate of impaired recovery. Low protein intake, iron deficiency, reduced caloric reserve, and sarcopenia may limit the capacity to recover after TAVI, contribute to persistent fatigue and disability, and increase the risk of recurrent hospitalization. Several studies support this framework. In the FRAILTY-AVR study, frailty assessment markedly improved risk stratification in older adults undergoing aortic valve replacement, and specific frailty instruments were associated with mortality and disability at one year [6]. Within the broader frailty construct, physical performance measures such as gait speed and the Short Physical Performance Battery (SPPB) are particularly attractive because they are objective, rapid, and closely linked to meaningful outcomes. The same applies to nutritional tools such as the Mini Nutritional Assessment Short Form (MNA-SF), which identify patients who are either frankly malnourished or already on a trajectory of nutritional decline. From a clinical standpoint, the relevance of physical performance and nutritional status in TAVI lies in three complementary features. First, both are common. Depending on the population studied and the tool used, reduced physical performance, frailty, sarcopenia, and nutritional risk affect a large proportion of TAVI candidates. Second, both are prognostically powerful. Frail or malnourished patients have consistently shown higher mortality, more disability, worse quality of life, and more readmissions after TAVI than fitter and nutritionally preserved patients [3,6,7]. Third, and most importantly, both are actionable. Unlike many non-modifiable predictors of outcome, physical performance and nutritional status can potentially be improved through structured intervention. This point is central to the rationale of IRON-TAVI. The current standard pre-TAVI work-up is highly effective in defining anatomy, procedural feasibility, and immediate procedural risk, but it does relatively little to optimize the global condition of the patient before and after the intervention. In routine practice, poor mobility, low muscle reserve, inadequate protein intake, and nutritional risk are frequently recognized but rarely targeted in a structured

manner. This gap may be especially important in patients waiting several weeks for TAVI, a period during which symptoms, inactivity, and nutritional decline may continue to worsen. Moreover, the early post-TAVI phase represents a window of opportunity: once the mechanical obstruction is relieved, the patient may be biologically more capable of responding to rehabilitation and nutritional repletion, provided that a structured program is actually implemented. There is a strong biological rationale for a combined intervention. Exercise training and nutritional support are not alternative strategies; they are synergistic. In older adults, exercise improves muscle strength, gait efficiency, balance, exercise tolerance, and confidence in daily activities. Nutritional optimization, particularly when it improves protein adequacy and corrects iron depletion or iron deficiency, may support muscle protein synthesis, functional recovery, and fatigue reduction. When the two strategies are combined, the chance of translating functional improvement into a measurable clinical benefit is likely greater than with either strategy alone. This concept is well established in geriatric medicine and increasingly supported in cardiovascular prevention and rehabilitation. Evidence from adjacent cardiovascular settings strengthens this view. In older adults after myocardial infarction, multidomain rehabilitation programmes combining exercise, nutritional counselling, and rigorous risk-factor management have shown improvements in physical performance, quality of life, and clinical outcomes [8,9]. In hospitalized frail cardiovascular patients, multicomponent interventions targeting physical weakness, nutrition, cognition, and anemia have proved feasible and clinically meaningful [10]. Although these populations are not identical to TAVI candidates, they share a common substrate of advanced age, frailty, multimorbidity, and impaired physiologic reserve. The success of multidomain strategies in these settings suggests that the same paradigm could be relevant in older adults undergoing TAVI. By contrast, direct evidence in TAVI candidates remains limited. Exercise-based cardiac rehabilitation after TAVI has shown encouraging effects on exercise capacity, walking distance, physical independence, frailty parameters, and quality of life, but the available literature remains heterogeneous in design, timing, supervision, and endpoints [11,12]. Most studies have been small, single-centre, and primarily focused on short-term functional outcomes rather than hard clinical events. The same applies to nutritional approaches: multiple observational studies indicate that nutritional impairment is associated with adverse outcome after TAVI, and meta-analytic evidence supports the prognostic role of nutritional status [7], yet there is still no definitive randomized trial specifically designed to test whether a structured combined exercise-and-supplement intervention can improve prognosis in this population. The limitations of prior studies are therefore clear. First, most available investigations have enrolled relatively small samples, making them underpowered to detect differences in mortality or rehospitalization. Second, intervention timing has been inconsistent, with some programmes beginning only after TAVI and others focusing exclusively on inpatient or rehabilitation settings. Third, the populations studied have often been heterogeneous with regard to frailty severity, nutritional impairment, and baseline physical performance.

Fourth, outcome assessment has frequently relied on disparate tools, limiting comparability across studies. Finally, the optimal integration of prehabilitation and early postprocedural rehabilitation remains undefined. These unresolved questions are clinically important. A purely post-TAVI programme may miss the chance to stabilize or modestly improve the patient during the waiting phase, whereas a purely pre-TAVI approach may fail to exploit the postprocedural window in which symptom relief allows greater engagement in recovery. Likewise, an exercise-only model may overlook the biological importance of nutritional repletion, while a nutrition-only model may fail to convert improved intake into better functional capacity. For this reason, the most coherent strategy for older frail TAVI candidates is a multidomain model spanning both sides of the procedure: conservative pre-TAVI conditioning followed by structured post-TAVI progression, coupled with pragmatic nutritional support across the same time frame.

From an implementation perspective, IRON-TAVI is designed around tools and interventions that are deliberately pragmatic. SPPB and MNA-SF can be administered quickly at the bedside or in the outpatient setting, allowing systematic identification of the target phenotype. The exercise intervention is built on a mixed model of supervised sessions and home-based activity, which is more scalable than traditional centre-based cardiac rehabilitation. The nutritional intervention combines individualized counselling with protocol-mandated iron/protein-rich oral supplementation, thereby addressing both diet quality and the practical barriers to adequate intake that are common in frail older adults. If effective, such a strategy would be highly translatable to routine TAVI pathways. The trial also addresses a broader conceptual issue in contemporary TAVI care. As TAVI expands to larger and older populations, success can no longer be judged by device implantation alone. A patient-centred TAVI pathway must seek to reduce the gap between technical success and meaningful recovery. In many older adults, the main therapeutic goal is not merely survival but survival with maintained autonomy, symptom relief, fewer readmissions, and acceptable quality of life. Physical performance and nutritional status lie at the centre of this goal. They help explain why some patients remain disabled or repeatedly hospitalized despite successful TAVI, and they represent plausible therapeutic targets through which prognosis may be improved. In summary, severe AS in older adults is not simply a valve disease but a syndrome in which valvular obstruction interacts with frailty, reduced physical performance, malnutrition, and sarcopenia. TAVI effectively treats the valvular lesion, but a substantial proportion of patients still fail to recover meaningfully after the procedure. Existing evidence strongly suggests that poor physical performance and nutritional impairment are common, prognostically relevant, and actionable, yet they are not systematically targeted in contemporary TAVI practice. The available intervention studies are promising but remain insufficient to define standard care. A randomized multicentre trial specifically evaluating a structured programme of exercise training combined with nutritional support across the pre- and post-TAVI phases is therefore timely and clinically justified.

Figure 1. The continuum of malnutition, frailty and sarcopenia [4].

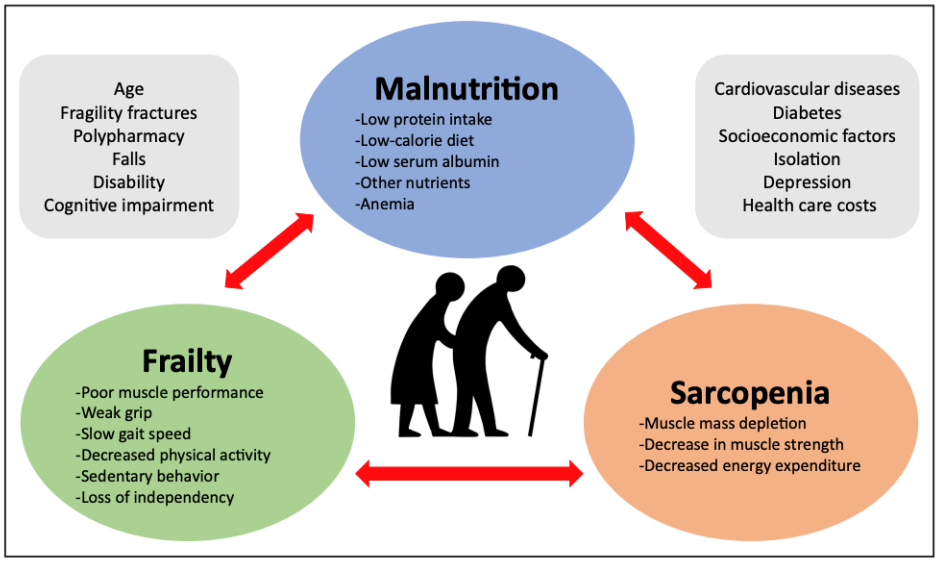


Table 1. Prevalence of poor physical performance, malnutrition, frailty and sarcopenia in TAVI patients.

Domain	Definition	Prevalence in TAVI population	References
Reduced physical performance	SPPB ≤8	40–70%	Stortecky et al., 2012; Afilalo et al., 2017
	Gait speed <0.8 m/s	30–60%	Afilalo et al., 2010; Schoenenberger et al., 2013
	6MWT reduced	50–80%	Pressler et al., 2016
Frailty	Fried / Rockwood scales	40–60%	Afilalo et al., 2017; Green et al., 2012
Malnutrition / risk	MNA (Mini Nutritional Assessment)	30–60% at risk; 10–20% malnourished	Fumagalli et al., 2026
Sarcopenia	EWGSOP criteria	30–50%	Shimura et al., 2019

1.1 What we know

- Patients undergoing TAVI are typically older, multimorbid, and frequently frail, with a high prevalence of reduced physical performance, nutritional risk, and sarcopenia.
- Frailty, malnutrition, and reduced physical performance are consistently associated with mortality, disability, and readmission after TAVI.
- A substantial minority of patients do not achieve a meaningful improvement in symptoms, autonomy, or quality of life after a technically successful TAVI procedure.
- Exercise-based and multidomain rehabilitation strategies are feasible in older cardiovascular populations and appear promising in the TAVI setting, especially when focused on functional recovery rather than procedure alone.
- Nutritional optimization is biologically plausible and clinically attractive because poor intake, protein inadequacy, and iron depletion are common in frail older adults.

1.2 What is missing

- A randomized multicentre clinical trial specifically designed for older TAVI patients with suboptimal physical performance and/or poor nutritional status.
- A structured intervention spanning both the pre-TAVI waiting phase and the early post-TAVI recovery phase.
- A pragmatic multidomain programme combining exercise training with protocol-driven nutritional support.
- Evidence on whether modification of physical performance and nutritional status can translate into fewer hard clinical events, rather than short-term functional gains only.

2 Rational supporting the conduction of the IRON-TAVI trial

Older patients undergoing transcatheter aortic valve implantation (TAVI) frequently show reduced physical performance and/or poor nutritional status. These conditions are associated with a worse prognosis despite procedural success. In particular, they are related to a higher risk of death, disability, and hospital readmission for cardiovascular causes. At the same time, both conditions are easy to identify in routine practice through simple bedside tools such as the Short Physical Performance Battery (SPPB) and the Mini Nutritional Assessment Short Form (MNA-SF). Despite their clinical relevance, reduced physical performance and poor nutritional status are not systematically targeted in the current management of patients candidate to TAVI. Therefore, an important gap in evidence remains. No randomized multicenter trial has clearly demonstrated whether a structured intervention based on exercise training combined with iron and protein-rich oral supplementation may improve clinical outcome in this setting. The IRON-TAVI trial was designed to address this unmet need. The rationale of the study relies on three main points. First, poor physical performance and malnutrition are common in older patients undergoing TAVI and identify a subgroup at higher risk. Second, these conditions are actionable. Third, the proposed intervention is feasible and based on components already tested by the study group in previous experiences focused on older cardiovascular patients, where exercise-based strategies showed good feasibility, safety, and adherence. In addition, the IRON-TAVI trial is supported by a pragmatic and reproducible design. Screening is based on simple instruments. The intervention is based on a mixed model including supervised sessions and home-based activity, combined with dietary supplementation. This approach may facilitate implementation in daily practice if the study results will be positive. The study is conducted as a prospective, randomized, multicenter trial with blinded adjudication of outcomes, in order to ensure methodological rigor and adequate generalizability. Taken together, these considerations support the conduction of the IRON-TAVI trial. The study will assess whether a multidomain intervention based on exercise training and iron/protein supplementation is superior to current standard of care in older patients with suboptimal physical performance and/or nutritional status undergoing TAVI.

3 STUDY ENDPOINTS

3.1 Primary clinical efficacy endpoint

The primary clinical efficacy endpoint is the 1-year cumulative occurrence of all-cause death, stroke, or hospital readmission for cardiovascular cause. Clinical events will be defined according to the VARC-3 consensus document, whenever applicable.

3.2 Secondary efficacy endpoints

Secondary efficacy endpoints are the cumulative occurrence of:

- all-cause death
- cardiovascular death
- stroke
- myocardial infarction
- hospital readmission for heart failure
- hospital readmission for any cardiovascular cause
- hospital readmission for any cause

Additional secondary efficacy endpoints are:

- change in physical performance assessed by Short Physical Performance Battery (SPPB)
- change in nutritional status assessed by Mini Nutritional Assessment Short Form (MNA-SF)
- change in sarcopenia risk assessed by Strength, Assistance with walking, Rise from a chair, Climb stairs, and Falls (SARC-F)
- change in body composition assessed by bioimpedance analysis
- quality of life assessed by EuroQol-5D (EQ-5D-5L)
- quality of life assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ)
- compliance to the multidomain intervention in the experimental arm.

3.3 Primary safety endpoint

The primary safety endpoint is the cumulative occurrence of adverse events related to exercise training or dietary supplementation. These include, but are not limited to, angina resurgence, heart failure worsening, bleeding, falls or traumatism related to exercise training, and worsening renal function or other clinically relevant adverse effects related to dietary supplementation.

3.4 Other safety endpoints

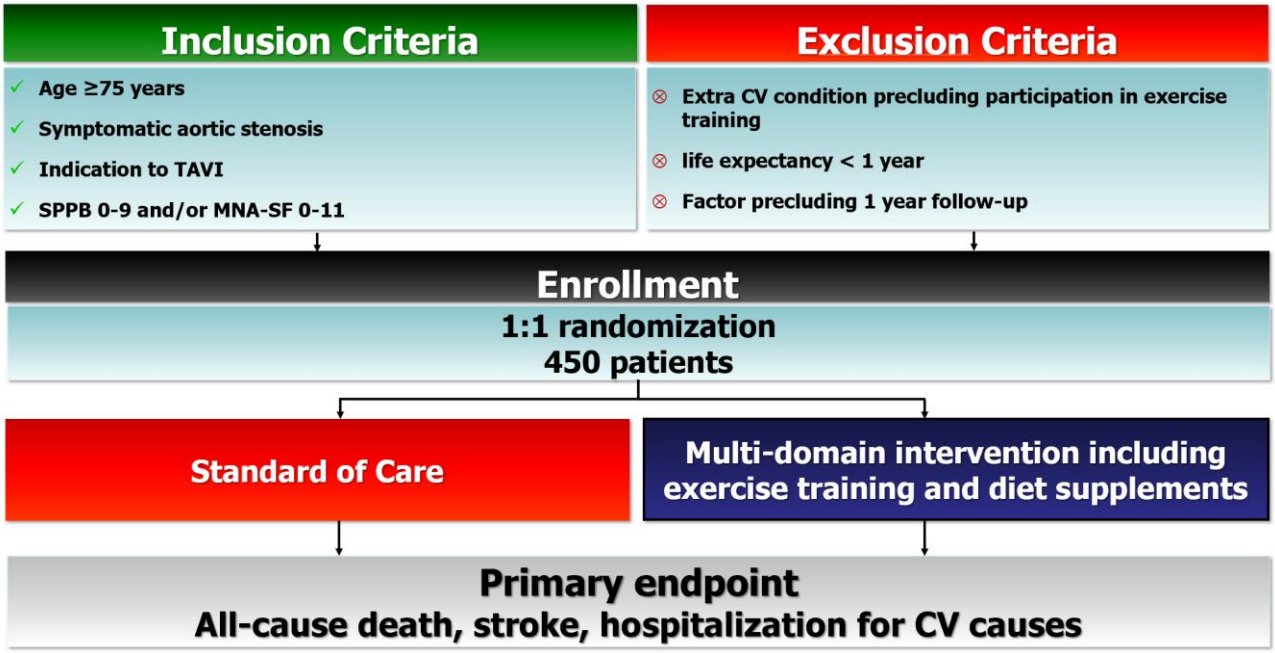
Other safety endpoints are:

- adverse events related to exercise training
- adverse events related to dietary supplementation
- worsening renal function
- falls and traumatism
- bleeding events
- compliance discontinuation due to intolerance or adverse events

4 STUDY DESIGN, SCREENING, INCLUSION AND RANDOMIZATION

4.1 Study design

The IRON-TAVI trial is an all-comers, prospective, randomized, multicenter, open-label trial with blinded adjudicated evaluation of outcomes (PROBE design). The study is designed to test the superiority of a multidomain intervention based on exercise training plus iron and protein-rich oral supplementation over current standard of care in older patients with symptomatic aortic stenosis candidate to transcatheter aortic valve implantation (TAVI) and presenting with reduced physical performance and/or poor nutritional status. After Heart Team indication to TAVI, patients will be screened for eligibility. Physical performance will be assessed by Short Physical Performance Battery (SPPB) and nutritional status by Mini Nutritional Assessment Short Form (MNA-SF). Patients with SPPB score <10 and/or MNA-SF score <12 who fulfill all inclusion and exclusion criteria and provide written informed consent will be randomized in a 1:1 fashion to one of the following study groups: i) multidomain intervention including exercise training and diet supplements (experimental arm), or ii) standard of care (control arm).



4.2 Identification of the participating centers

The Steering Committee will identify and invite potential participating centers. Centers interested in participation must document adequate experience in the management of patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI). Participating centers must also demonstrate the availability of local facilities and personnel for patient screening, follow-up, assessment of physical

performance and nutritional status, and delivery of the study intervention. To be eligible, each center must have: i) an established Heart Team for indication to TAVI; ii) an adequate volume of TAVI procedures; iii) previous experience in randomized clinical trials; iv) the availability of trained investigators for Short Physical Performance Battery (SPPB) and Mini Nutritional Assessment Short Form (MNA-SF) assessment; v) access to a structured network with cardiac rehabilitation units and/or sports medicine facilities for the exercise intervention; and vi) the capability to ensure study follow-up and data collection according to protocol. The coordinating center will verify the characteristics of the candidate centers before activation. All participating centers will receive specific training on the study protocol, study procedures, use of the electronic Case Report Form (eCRF), adverse event reporting, and conduct of the multidomain intervention. Center activation will occur only after confirmation that all protocol requirements are fulfilled.

4.3 Screening of the patients

After Heart Team indication to transcatheter aortic valve implantation (TAVI), consecutive patients will be screened for study eligibility. Screening will be performed before the procedure and after verification of the clinical indication to TAVI. The study is intended to enroll older patients with symptomatic aortic stenosis and reduced physical performance and/or poor nutritional status. Screening evaluation will include collection of demographic and clinical characteristics, review of medical history, assessment of eligibility criteria, and evaluation of physical performance and nutritional status. Physical performance will be assessed by the Short Physical Performance Battery (SPPB). Nutritional status will be assessed by the Mini Nutritional Assessment Short Form (MNA-SF). Patients with SPPB score <10 and/or MNA-SF score <12 will be considered potentially eligible for enrollment, provided that all inclusion criteria are satisfied and no exclusion criterion is present. The SPPB includes three domains, each scored from 0 to 4 points: standing balance, walking speed, and chair sit-to-stand. The total score ranges from 0 to 12, with lower values indicating worse physical performance. The MNA-SF is a brief tool for the assessment of malnutrition risk in older adults and includes six items exploring food intake, weight loss, mobility, disease acuity, body mass index, and cognitive or mood impairment. Two other measures will be performed: a tool for sarcopenia (SARC-F) and the evaluation with bioimpedance. Screening will also include verification of the exclusion criteria, with particular attention to non-cardiovascular comorbidity reducing life expectancy to less than 1 year, factors precluding 1-year follow-up, and extra-cardiovascular conditions precluding participation in the exercise sessions. Consecutive screening must be ensured at each participating center in order to minimize selection bias. After confirmation of eligibility, the study investigator will discuss the trial with the patient and, if appropriate, with relatives or caregivers. Only patients providing written informed consent will undergo randomization. Screening and eligibility data will be recorded in the electronic Case Report Form (eCRF).

4.4 Study discussion and informed consent

The study investigator will discuss the study with the patient and, when appropriate, with relatives or caregivers. The study investigator will explain the study design, objectives, procedures, follow-up schedule, and the characteristics of the two study arms. The potential benefits and risks related to study participation will be detailed, including those related to exercise training and dietary supplementation. Available alternatives will also be explained. Adequate time will be given to the patient to ask questions and to decide whether to participate. Written informed consent must be obtained before randomization and before any study-specific procedure not included in routine clinical practice. Only patients providing written informed consent can be randomized. Participation in the study is voluntary. The patient may refuse participation or withdraw consent at any time, without any consequence on the standard clinical management and indication to transcatheter aortic valve implantation (TAVI). All informed consent procedures will be conducted in accordance with Good Clinical Practice and local regulatory requirements.

4.5 Randomization

Randomization will be performed after confirmation of eligibility criteria and after signature of the informed consent. Randomization will be performed centrally using an internet-based system. The patient identification number (Patient ID) and treatment allocation will be assigned by the central randomization system.
Patients will be randomized in a 1:1 fashion to one of the following study arms:

- EXPERIMENTAL ARM: multi-domain intervention including exercise training and iron/protein-rich oral supplementation
- CONTROL ARM: standard of care.

Treatment allocation will be assigned according to a computer-generated randomization list stratified by center, sex (male vs female), baseline physical performance assessed by SPPB (cut-off at 7), and baseline nutritional status assessed by MNA-SF (cut-off at 8). All patients who are randomized are irrevocably in the study, whether or not they are subsequently found to be fully eligible, or actually receive the allocated treatment. Therefore, all randomized patients must be followed until the prespecified study end date, unless consent is withdrawn.

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4.6 Measures to minimize/avoid bias

The trial is conducted under an open-label design. Blinding of patients and investigators is not feasible because of the nature of the intervention, which includes exercise training and dietary supplementation in the experimental arm and standard of care in the control arm. To minimize the risk of bias, several measures will

be adopted. First, randomization will be performed centrally through an internet-based system, according to a computer-generated randomization list stratified by center, sex, SPPB value, and MNA-SF value. This approach will ensure balance between treatment groups for the main baseline variables related to prognosis and intervention effect. Second, consecutive screening and enrollment of patients will be promoted at each participating center. Screening and eligibility data will be recorded in the electronic Case Report Form (eCRF). This approach is intended to reduce selection bias and to improve transparency of the enrollment process. Third, all study endpoints and adverse events will be adjudicated by an independent Clinical Event Committee blinded to treatment allocation. Endpoint definitions will be prespecified in the protocol and applied uniformly across study groups. The adjudication results will be binding for the final analysis. Fourth, safety will be monitored by an independent Data Safety Monitoring Board (DSMB), which will periodically review adverse events and study conduct. The DSMB will have the authority to recommend study interruption in case of safety concerns. Finally, the primary analysis will be performed according to the intention-to-treat principle, including all randomized patients according to assigned treatment. This approach will preserve the benefits of randomization and limit potential bias related to treatment crossover or incomplete adherence.

5 STUDY POPULATION

5.1 Inclusion criteria

Patients must fulfill all the following inclusion criteria to be eligible for the study:

1. Age ≥75 years
2. Symptomatic aortic stenosis
3. Indication to transcatheter aortic valve implantation (TAVI) confirmed by the Heart Team
4. Reduced physical performance defined as Short Physical Performance Battery (SPPB) score <10 and/or poor nutritional status defined as Mini Nutritional Assessment Short Form (MNA-SF) score <12
5. Written informed consent

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5.2 Exclusion criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Non-cardiovascular co-morbidity reducing life expectancy to <1 year
2. Any factor precluding 1-year follow-up
3. Extra-cardiovascular condition precluding participation in the exercise training sessions
4. Refusal or inability to provide written informed consent.

6 STUDY PROCEDURES

6.1 General information regarding aortic stenosis diagnosis, TAVI indication and Heart Team discussion

All patients considered for inclusion in the study must have a diagnosis of severe symptomatic aortic stenosis and an indication to transcatheter aortic valve implantation (TAVI) established according to current international guidelines and local standards of care [2]. The diagnosis of aortic stenosis must be based on the integration of clinical presentation and multimodality imaging, with transthoracic echocardiography representing the main diagnostic tool. Additional diagnostic tests may be performed when required to confirm stenosis severity, clarify flow-gradient pattern, assess left ventricular function, or resolve diagnostic uncertainty. The indication to TAVI must be discussed and confirmed by the local Heart Team. The Heart Team should include, at minimum, interventional cardiologists, cardiac surgeons, imaging specialists, with the possible involvement of geriatricians and other specialists according to the clinical characteristics of the patient. The Heart Team discussion must take into account symptoms, aortic valve disease severity, anatomical suitability, comorbidities, frailty profile, life expectancy, procedural risk, expected benefit from valve replacement, and patient preference. The choice of TAVI as the treatment strategy must be based on an overall clinical judgment integrating guideline recommendations, anatomical feasibility, procedural considerations, and the expected balance between risks and benefits. Device selection, vascular access, peri-procedural management, and timing of the procedure will be left to the treating Heart Team and performed according to current clinical practice. Only patients with a confirmed indication to TAVI after formal Heart Team evaluation may undergo study screening and randomization.

6.2 Experimental arm: general description

The experimental arm consists of a multidomain intervention including exercise training and nutritional support. The intervention starts after randomization and before transcatheter aortic valve implantation (TAVI), continues during the early post-procedural phase, and is maintained up to 3 months after TAVI. The intervention is tailored according to baseline physical performance, nutritional status, clinical condition, symptoms, and temporal relationship with the TAVI procedure. The intervention is based on two synergistic components:

i) a personalized exercise training program combining supervised sessions and home-based activity;

ii) a nutritional strategy including individualized dietary counselling and iron/protein-rich oral supplementation.

During the pre-TAVI phase, the main aim is to improve mobility, muscle strength, exercise tolerance, and nutritional intake while maintaining clinical stability and avoiding symptom worsening. During the post-TAVI

phase, the main aim is to promote functional recovery, restore confidence in daily activities, improve physical performance, and optimize nutritional repletion. Adherence to the intervention will be systematically monitored during study visits and phone contacts.

6.3 Experimental arm: exercise training

The exercise training intervention consists of a personalized, low-intensity to moderate-intensity, mixed program combining supervised sessions with a structured home-based prescription. The program is specifically designed for older patients with severe symptomatic aortic stenosis undergoing transcatheter aortic valve implantation (TAVI), with the dual aim of pre-procedural conditioning and post-procedural functional recovery. The intervention is inspired by the exercise models previously adopted in frail and older cardiovascular patients in the PIpELINe and SAMCRO experiences, but is adapted to the greater clinical vulnerability, symptom burden, and hemodynamic limitations of patients with severe aortic stenosis [14, 15].
The intervention starts after randomization and before TAVI. It continues after the procedure, once the patient is considered clinically stable by the treating team, and is maintained up to 3 months after TAVI. The exercise prescription is individualized according to baseline Short Physical Performance Battery (SPPB), nutritional status, symptoms, overall frailty profile, comorbidities, and temporal relationship with the procedure. Particular attention will be paid to dyspnea, fatigue, dizziness, presyncope, mobility limitation, and fear of movement, which are common in this population and may markedly change after TAVI.
The exercise program is divided into two phases.

- **Pre-TAVI phase**

During the period from randomization to TAVI, the intervention aims to preserve mobility, reduce sedentary behavior, improve gait efficiency, maintain or modestly improve lower-limb strength, and prepare the patient for a better functional recovery after the procedure. Because of the presence of severe aortic stenosis, exercise intensity in this phase will remain conservative, symptom-limited, and low to moderate. Training will privilege walking-based activity, sit-to-stand exercises, balance exercises, mobility work, and light calisthenics. Abrupt increases in workload, sustained isometric effort, and any activity inducing marked dyspnoea, angina, dizziness, or presyncope will be avoided.

- **Post-TAVI phase**

After TAVI, and only after confirmation of clinical stability by the treating physicians, the same intervention will be progressively intensified. The main goals of the post-procedural phase are to restore confidence in movement, improve exercise tolerance, recover autonomy in daily activities, increase walking time, and enhance lower-extremity performance, balance, and overall physical function. Progression will be gradual and individualized according to symptoms, blood pressure response, heart rate, fatigue, and global tolerance. This

two-step approach reflects the major physiological transition that occurs before and after relief of valvular obstruction and represents a key distinctive feature of the IRON-TAVI intervention.

Each supervised session will be delivered by trained study personnel with experience in exercise prescription for older cardiovascular patients. Sessions will be performed in an outpatient setting, cardiac rehabilitation facility, sports medicine service, or equivalent supervised environment according to local organization. Each supervised session will include: i) symptom review and interim clinical evaluation; ii) measurement of blood pressure and heart rate; iii) brief warm-up and mobility exercises; iv) walking-based aerobic training; v) functional exercises focused on lower-limb strength, balance, transfers, and posture; vi) cool-down; and vii) reinforcement of the home-based prescription and counselling on physical activity in daily life. This general structure is consistent with the pragmatic and reproducible models used in previous trials. The home-based program will be prescribed after each supervised session and periodically updated. Patients will be encouraged to perform regular walking activity and a short series of functional exercises at home. Depending on baseline performance and clinical tolerance, home-based activity will include walking, sit-to-stand exercises, lower-limb strengthening without external load or with minimal load, balance tasks near stable support, and mobility exercises for trunk and upper limbs. Family members and caregivers may be involved, when appropriate, to improve adherence and safety. When an on-site session cannot be performed, remote contact by phone or telemedicine may be used to reinforce adherence and adjust the home-based program, consistently with the pragmatic strategy already adopted in previous multidomain intervention studies. Exercise intensity will be prescribed according to FITT principles and primarily guided by perceived exertion. In general, exercise will be maintained within a low-to-moderate or moderate intensity domain, avoiding high-intensity efforts. During the pre-TAVI phase, the target perceived exertion will usually correspond to 10 to 12 on the Borg scale. During the post-TAVI phase, the target perceived exertion may be progressively increased to 11 to 13 on the Borg scale, provided that symptoms and hemodynamic tolerance remain acceptable. The prescription will be individualized and may be reduced in more symptomatic or frailer patients. Compared with previous exercise programs used in post-myocardial infarction or ANOCA settings, the IRON-TAVI intervention is intentionally more conservative before the procedure and more progressive after TAVI. Progression or de-intensification of the training load will be based on functional performance, symptom burden, patient confidence, and overall tolerance. A session may be postponed, simplified, or interrupted in case of angina, worsening dyspnea, dizziness, presyncope, syncope, decompensated heart failure, clinically significant arrhythmias, acute illness, trauma, uncontrolled hypertension, or any other condition judged by the investigator to make exercise temporarily unsafe. Particular caution will be adopted in the pre-TAVI phase and in the first period after the procedure. Safety monitoring and temporary treatment interruption are consistent with the

principles already applied in prior structured exercise interventions in older cardiovascular patients. Adherence to exercise training will be assessed by recording attendance at supervised sessions and by structured collection of information on home-based activity during study visits and interim contacts. Compliance will be expressed as the proportion of completed supervised sessions and the proportion of prescribed home-based sessions reported as performed. Reasons for temporary interruption or permanent discontinuation will be documented. The coordinating center will provide training to local personnel and a standardized operational manual in order to ensure homogeneous implementation of the intervention across centers. This approach is coherent with the multicenter implementation strategy of PIpELINe and with the structured multidomain approach used in SAMCRO [14, 15]

Exercise training intervention according to FITT principles in the IRON-TAVI trial

Component	Pre-TAVI phase	Post-TAVI phase
Frequency	Supervised sessions according to study schedule; home-based activity at least 3 times per week	Supervised sessions according to study schedule; home-based activity at least 4 to 5 times per week
Intensity	Low to moderate, symptom-limited, usually Borg 10–12	Moderate, symptom-limited, usually Borg 11–13
Time	Walking-based aerobic activity about 10–20 min per session plus short functional exercises	Walking-based aerobic activity about 20–30 min per session plus functional exercises
Type	Walking, mobility exercises, sit-to-stand, balance exercises, light calisthenics, posture and transfer training	Walking, mobility exercises, sit-to-stand, balance exercises, calisthenics, progressive functional strengthening
Progression	Conservative progression; no abrupt increase in workload before TAVI	Gradual progression after TAVI according to symptoms, tolerance, and recovery
Warm-up / cool-down	Mandatory, gradual, with emphasis on symptom monitoring	Mandatory, gradual, with emphasis on symptom monitoring
Main objective	Prehabilitation, preservation of mobility, reduction of sedentary behavior, preparation for TAVI	Functional recovery, improvement in exercise tolerance, autonomy, and physical performance

This FITT structure is conceptually derived from the supervised plus home-based framework and from the emphasis on individualized progression already used in PIpELINe and SAMCRO, but adapted to the clinical course of severe aortic stenosis treated with TAVI.

Schedule and content of supervised exercise sessions in the IRON-TAVI trial

Time point	Phase	Main aims	Mandatory session content
Baseline / randomization visit	Pre-TAVI	Initial exercise prescription, safety evaluation, education	Symptom review, blood pressure and heart rate, baseline mobility and functional assessment, first supervised low-intensity session, home-based prescription
Pre-TAVI interim session(s)	Pre-TAVI	Maintain mobility, prevent deconditioning, reinforce adherence	Symptom review, blood pressure and heart rate, warm-up, walking-based exercise, sit-to-stand and balance work, cool-down, home-based update
Early post-TAVI session	Post-TAVI	Safe reactivation after procedure, restore confidence in movement	Clinical stability check, symptom review, blood pressure and heart rate, gentle mobility and walking activity, low-intensity functional work, home-based reactivation
Intermediate post-TAVI session(s)	Post-TAVI	Increase exercise tolerance and daily autonomy	Symptom review, blood pressure and heart rate, walking-based aerobic training, functional strengthening, balance training, counselling on daily activity
Final 3-month session	Post-TAVI	Consolidate behavioural change and long-term activity habit	Symptom review, blood pressure and heart rate, reassessment of performance, final progression of walking and functional program, long-term home-based advice

The exact number and timing of sessions may follow the study schedule defined in the protocol, but all sessions should preserve the same general structure and the same two-phase rationale, namely pre-TAVI conditioning and post-TAVI recovery/progression. This is in line with the session-based architecture used in PIpELINe and the supervised-plus-home framework used in SAMCRO.

Timing of physical activity sessions.

Time point	Phase	Main aims	Mandatory session content
Baseline / randomization visit	Pre-TAVI	T0, 30±10 days before TAVI procedure	Symptom review, blood pressure and heart rate, baseline mobility and functional assessment, first supervised low-intensity session, home-based prescription
Home-based physical activity program			
Pre-TAVI interim session(s) OPTIONAL	Pre-TAVI	T1, 15±5 days before TAVI procedure	Symptom review, blood pressure and heart rate, warm-up, walking-based exercise, sit-to-stand and balance work, cool-down, home-based update
Home-based physical activity program			
Early post-TAVI session	Post-TAVI	T2, 30±10 days after TAVI procedure	Clinical stability check, symptom review, blood pressure and heart rate, gentle mobility and walking activity, low-intensity functional work, home-based reactivation
Home-based physical activity program			
Intermediate post-TAVI session(s)	Post-TAVI	T3, 60±10 days after TAVI procedure	Symptom review, blood pressure and heart rate, walking-based aerobic training, functional strengthening, balance training, counselling on daily activity
Home-based physical activity program			
Final 3-month session	Post-TAVI	T3, 90±10 days after TAVI procedure	Symptom review, blood pressure and heart rate, reassessment of performance, final progression of walking and functional program, long-term home-based advice
Long-term home-based physical activity			

6.4 Experimental arm: dietary supplementation and nutritional intervention

The nutritional component of the experimental arm consists of individualized nutritional counselling combined with iron/protein-rich oral supplementation. The intervention is specifically designed for older patients with severe symptomatic aortic stenosis undergoing transcatheter aortic valve implantation (TAVI), a population frequently characterized by reduced nutritional reserve, inadequate protein intake, low appetite, sarcopenia risk, and iron deficiency or iron-depleted status. These factors may contribute to reduced physical performance, fatigue, impaired recovery, and increased vulnerability before and after the procedure. The nutritional intervention starts after randomization and before TAVI, and continues after the procedure up to 3 months after TAVI. The rationale of this two-phase strategy is to optimize nutritional condition before the procedure and to support recovery, muscle function, and global functional status after relief of valvular obstruction. The intervention is individualized according to baseline Mini Nutritional Assessment Short Form (MNA-SF), body weight, recent weight variation, appetite, renal function, hemoglobin, iron profile, comorbidities, and overall frailty profile. At baseline, each patient assigned to the experimental arm will undergo a structured nutritional evaluation. This evaluation will include assessment of MNA-SF, body weight, body mass index, bioimpedance analysis, recent involuntary weight loss, appetite, swallowing difficulties if present, gastrointestinal symptoms, and usual dietary habits. Available laboratory data, including hemoglobin and iron parameters, will be reviewed. The nutritional interview will also explore meal pattern, protein distribution during the day, barriers to adequate nutrition, social support, and factors potentially limiting adherence, such as fatigue, poor dentition, early satiety, gastrointestinal intolerance, and difficulty in meal preparation. This structured and pragmatic nutritional approach is consistent with the counselling framework previously used in SAMCRO and with the multidomain rehabilitation strategy used in PIpELINe [14, 15]. Nutritional counselling will be focused on feasibility and adequacy rather than on complex dietary schemes. Patients will be encouraged to maintain regular meal timing, avoid prolonged fasting, ensure sufficient caloric intake, and improve the quality and distribution of protein intake across the day. Particular emphasis will be placed on adequate breakfast and lunch protein content, because protein intake in older patients is often concentrated in a single meal and may therefore be suboptimal for muscle maintenance. When possible, the dietary pattern will remain close to a Mediterranean model, but adapted to the needs of frail older adults, with specific attention to practicality, tolerance, and preservation of appetite. The counselling will privilege high-quality protein sources, adequate hydration, and simple nutritional solutions compatible with the patient's functional and social condition. In addition to dietary counselling, all patients in the experimental arm will receive iron/protein-rich oral supplementation according to protocol. The aim of supplementation is to support protein intake and iron repletion in a standardized and pragmatic manner. Supplementation will start after

randomization and will continue before and after TAVI throughout the intervention period, unless it is temporarily suspended or permanently discontinued because of intolerance, adverse events, investigator judgment, or major change in clinical condition. This component is directly aligned with the original design of the IRON-TAVI project. The oral supplementation regimen will be protocol-mandated and standardized across centers (es. “Meritene forza e vitalità”, Nestle). The supplement should provide a combined nutritional support including protein enrichment and iron content, with administration in one or more daily doses according to the operational manual. The exact composition, formulation, timing, and possible alternatives will be prespecified in the study operational documents in order to guarantee consistency across sites. In the protocol, however, the supplementation strategy is intentionally described in functional terms, namely as an iron/protein-rich oral supplementation aimed at correcting or attenuating nutritional deficits and supporting physical recovery, rather than as a brand-specific intervention. The supplementation regimen may be adapted according to tolerance and clinical profile. In patients with reduced appetite or poor meal completion, supplementation may be preferentially administered between meals or during the part of the day associated with better intake. In patients with gastrointestinal sensitivity, the daily dose may be split to improve tolerance. In patients with renal dysfunction, the nutritional strategy may require adjustment of total protein load according to clinical judgment. These pragmatic adaptations are consistent with the individualized nutritional approach previously adopted in PIpELINe and SAMCRO [14, 15].

The nutritional strategy will differ in emphasis between the pre- and post-TAVI phases.

- **Pre-TAVI phase.**

The main goals will be to prevent further nutritional decline, improve energy and protein intake, reduce the effect of low appetite or fatigue on oral intake, and initiate iron/protein supplementation before the procedure. In this phase, the intervention will privilege simplicity, tolerability, and continuity, as patients may still be symptomatic because of severe aortic stenosis.

- **Post-TAVI phase.**

After the procedure, once the patient is clinically stable, the nutritional intervention will focus on recovery of muscle function, support of rehabilitation, increase in protein adequacy, and continuation of oral iron/protein supplementation. The post-TAVI phase is expected to provide a more favourable physiological window for nutritional recovery because symptoms often improve and daily activity may progressively increase.

Follow-up reassessment of the nutritional intervention will be performed during scheduled study visits and interim contacts. At each time point, body weight, appetite, adherence, and tolerability will be reviewed. Particular attention will be paid to gastrointestinal symptoms, including nausea, abdominal discomfort, constipation, diarrhoea, and poor palatability, as well as to possible laboratory evidence of worsening renal

function or other relevant intolerance. Supplementation may be temporarily withheld or permanently discontinued if deemed clinically inappropriate or poorly tolerated. All modifications will be documented. Adherence to the nutritional intervention will be assessed by recording completion of counselling sessions and by structured collection of information regarding supplement intake during follow-up visits and interim contacts. Compliance to supplementation will be expressed as the proportion of prescribed doses reportedly taken during the intervention period. The reasons for temporary interruption, dose reduction, or permanent discontinuation will be documented in the electronic Case Report Form. As for the exercise component, the coordinating center will provide a standardized nutritional intervention manual to all participating centers in order to improve consistency of implementation. This approach is coherent with the structured multidomain methodology adopted in the previous PIpELINe and SAMCRO experiences [14, 15].

Nutritional intervention and dietary supplementation in the IRON-TAVI trial

Component	Description
General strategy	Individualized nutritional counselling plus iron/protein-rich oral supplementation
Timing	Starts after randomization, continues before TAVI and up to 3 months after TAVI
Baseline assessment	MNA-SF, body weight, body mass index, recent weight variation, appetite, dietary habits, barriers to adequate intake, renal function, hemoglobin and iron profile when available
Main pre-TAVI aims	Prevent further nutritional decline, improve protein and energy intake, initiate supplementation, maintain tolerability and continuity
Main post-TAVI aims	Support recovery, improve protein adequacy, continue iron/protein supplementation, favor muscle and functional recovery
Dietary counselling	Pragmatic counselling focused on meal regularity, adequate caloric intake, protein distribution during the day, hydration, and feasible Mediterranean-style food choices adapted to frail older adults
Supplementation	Protocol-mandated iron/protein-rich oral supplementation administered in a standardized daily regimen according to the study operational manual
Possible adaptations	Splitting daily dose, between-meal administration, adjustment according to renal function, appetite, gastrointestinal tolerance, and overall clinical condition
Monitoring	Body weight, appetite, adherence, gastrointestinal symptoms, renal function and overall tolerability at study visits and interim contacts
Temporary interruption / discontinuation	Allowed in case of intolerance, relevant gastrointestinal symptoms, worsening renal function, major clinical instability, or investigator judgment
Adherence assessment	Recording of counselling completion and proportion of prescribed supplement doses reportedly taken

6.5 Control arm

Patients randomized to the control arm will receive standard of care according to current clinical practice for older patients with severe symptomatic aortic stenosis undergoing transcatheter aortic valve implantation (TAVI). Clinical management, timing of the procedure, device selection, vascular access, peri-procedural management, and follow-up will be left to the treating physicians and to the local Heart Team according to current guidelines and institutional standards. Before TAVI, patients allocated to the control arm will receive general advice to maintain regular physical activity as tolerated and to follow a balanced diet according to routine practice. After TAVI, patients will continue standard post-procedural care and routine follow-up according to local standards. No structured multidomain intervention will be delivered in the control arm. In particular, patients randomized to the control group will not undergo the supervised exercise training program, the protocol-mandated home-based exercise prescription, or the protocol-mandated iron/protein-rich oral supplementation planned for the experimental arm. Optimization of medical therapy, management of comorbidities, and nutritional or rehabilitative prescriptions considered clinically necessary by the treating physicians will remain allowed, as part of usual care. However, no structured study-driven program of exercise training or nutritional supplementation will be provided. This approach is intended to reflect routine clinical management and to allow comparison between the experimental multidomain strategy and current standard practice. All patients in the control arm will undergo the same study follow-up schedule and endpoint assessment as patients randomized to the experimental arm. Clinical events and adverse events will be collected and adjudicated according to protocol.

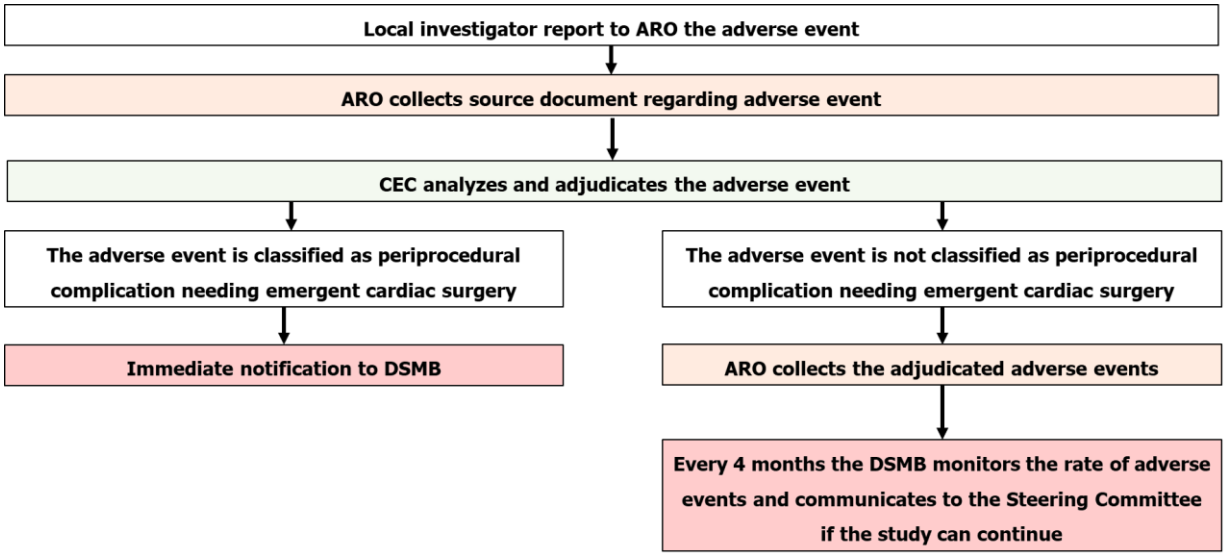
6.6 Follow-up

All randomized patients will undergo study follow-up from the time of randomization. Follow-up visits will be scheduled every 6 months according to protocol. The primary clinical efficacy endpoint will be assessed at 1 year from randomization. Follow-up will be performed irrespective of the assigned treatment arm and, whenever possible, irrespective of the degree of adherence to the study intervention. The aim of follow-up is to collect data on clinical status, study endpoints, adverse events, and adherence to the assigned strategy. All randomized patients will be followed until the prespecified study end date, unless consent is withdrawn. At each follow-up visit, investigators will assess vital status, occurrence of hospital admissions, cardiovascular events, cerebrovascular events, myocardial infarction, and adverse events related to exercise training or dietary supplementation, when applicable. In addition, compliance with cardiovascular medical therapy and major laboratory data will be reviewed according to clinical availability. Physical performance, nutritional status, and quality of life will be reassessed according to the study schedule using the prespecified study instruments. In particular, physical performance will be evaluated by Short Physical Performance Battery (SPPB), nutritional

status by Mini Nutritional Assessment Short Form (MNA-SF), SARC-F, Bioimpedence analysis and quality of life by EuroQol-5D (EQ-5D-5L) and Kansas City Cardiomyopathy Questionnaire (KCCQ). For patients randomized to the experimental arm, follow-up visits will also include assessment of adherence to the exercise training program and to iron/protein-rich oral supplementation, as well as review of tolerance and possible reasons for temporary interruption or permanent discontinuation. Whenever an on-site visit cannot be performed, follow-up information may be collected by phone contact, review of medical records, or contact with relatives or caregivers, according to local practice and data availability. Source documentation for all relevant clinical events will be collected for adjudication according to protocol.

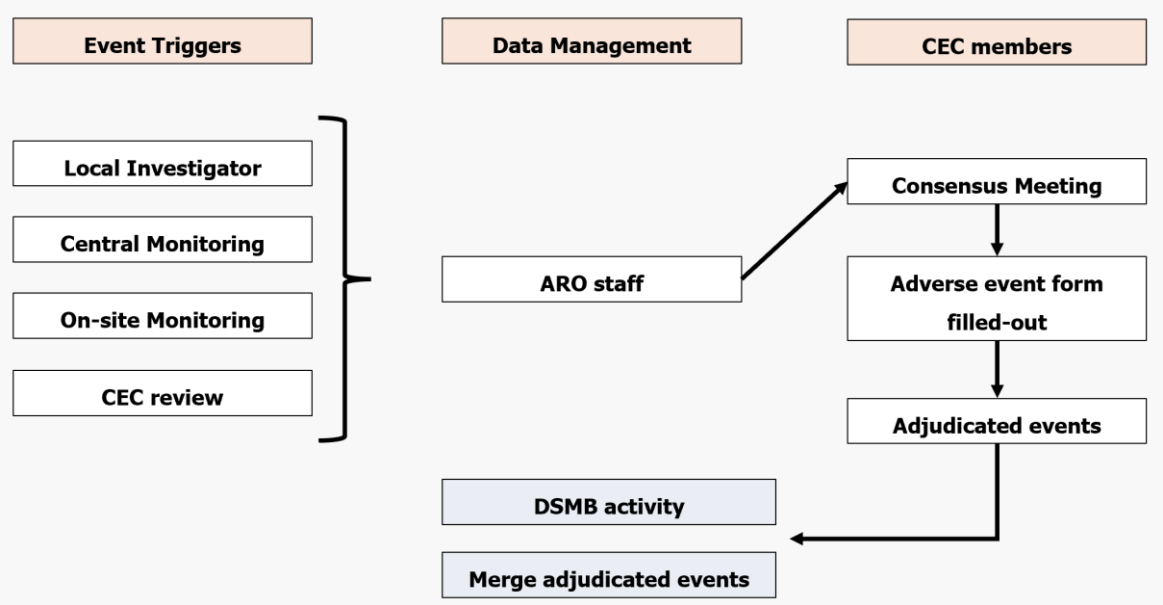
6.7 Study collection of adverse events

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.



6.8 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.



6.9 Role of the Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will oversee patient safety and study conduct throughout the trial. The DSMB will periodically review recruitment, adherence to the protocol, completeness of follow-up, and the occurrence of adverse events in the study population. Particular attention will be paid to adverse events potentially related to exercise training and dietary supplementation. The DSMB will have access to updated safety information and may request additional analyses whenever considered necessary for the protection of study participants. The DSMB will evaluate whether the frequency, severity, or pattern of adverse events raises concerns regarding the continuation of the study or of specific study procedures. The DSMB may recommend continuation of the trial without modifications, temporary suspension, protocol changes, or early termination of the study if relevant safety concerns emerge. The functioning rules, timing of meetings, and reporting procedures of the DSMB will be defined before study start in a dedicated charter or operational document. The DSMB will remain independent from the Steering Committee and from the investigators directly involved in patient enrollment, intervention delivery, endpoint adjudication, and final statistical analysis.

7 STUDY DEFINITIONS

7.1 Short Physical Performance Battery

The Short Physical Performance Battery (SPPB) is a standardized, objective tool used to assess lower-extremity physical performance in older adults. It is easy to administer, requires limited equipment, can be completed in a few minutes, and has demonstrated strong prognostic value in different cardiovascular settings [14]. In the IRON-TAVI trial, the SPPB is used to identify patients with reduced physical performance at baseline and to reassess changes in functional status during follow-up. The SPPB includes three domains:

i) standing balance,

ii) gait speed,

iii) chair sit-to-stand performance.

Each domain is scored from 0 to 4 points, with higher values indicating better performance. The total SPPB score ranges from 0 to 12. Lower scores indicate worse physical performance. In general, values of 10 to 12 are considered indicative of preserved physical performance, whereas lower values identify progressive degrees of impairment. In the IRON-TAVI trial, a score <10 is considered consistent with reduced physical performance and represents one of the inclusion criteria. The three components of the SPPB are defined as follows:

Balance test

The patient is asked to maintain three standing positions of increasing difficulty: side-by-side stand, semi-tandem stand, and tandem stand. Performance is scored according to the ability to maintain each position for the prespecified time.

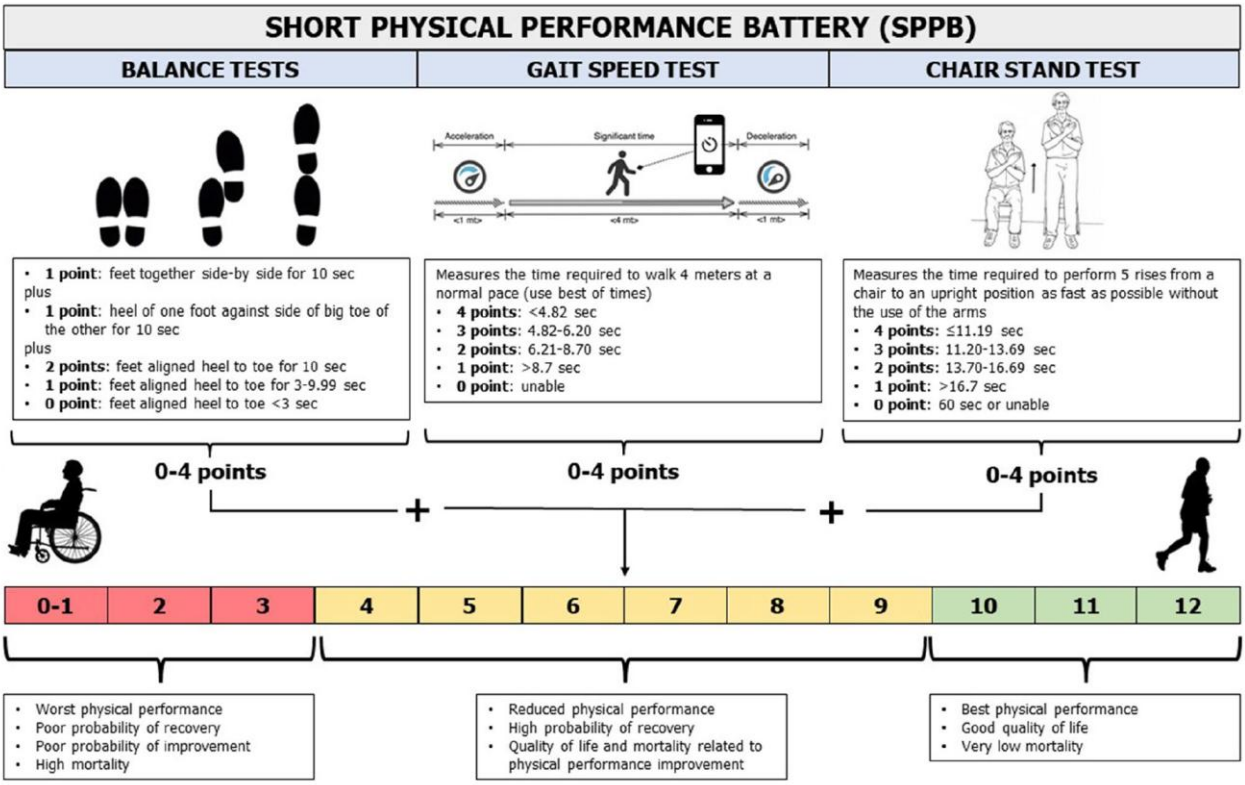
Gait speed test

The patient is asked to walk a short distance at usual pace. The time required to complete the walk is recorded and converted into the corresponding score according to standard SPPB criteria.

Chair stand test

The patient is asked to rise from a chair and sit down five times as quickly as possible without using the arms, if feasible. The time required to complete the test is recorded and scored according to standard SPPB criteria.

The SPPB will be administered by trained study personnel according to a standardized procedure. To ensure consistency across participating centers, investigators will receive specific training on test administration and scoring. The test should be performed in a safe environment and may be interrupted if symptoms or clinical instability occur.



7.2 Mini Nutritional Assessment – Short Form

The Mini Nutritional Assessment – Short Form (MNA-SF) is a validated, easy-to-use screening tool designed to identify older adults who are at risk of malnutrition or who are already malnourished. It is widely used in clinical practice and research in geriatric and cardiovascular populations and has demonstrated good predictive value for adverse outcomes, including hospitalization, functional decline, and mortality [11, 16]. In the IRON-TAVI trial, the MNA-SF is used at baseline to identify patients with poor nutritional status or at nutritional risk and to monitor changes over time in response to the nutritional intervention. The MNA-SF consists of 6 items covering key domains of nutritional status:

i) food intake,

ii) recent weight loss,

iii) mobility,

iv) psychological stress or acute disease,

v) neuropsychological problems,

vi) body mass index (BMI) or calf circumference, when BMI is not available.

Each item is scored and the scores are summed to obtain a total score ranging from 0 to 14, with higher values indicating better nutritional status. Interpretation of the total score is as follows:

- 12 to 14 points: normal nutritional status
- 8 to 11 points: at risk of malnutrition
- 0 to 7 points: malnourished

In the IRON-TAVI trial, an MNA-SF score <12 is considered consistent with poor nutritional status and represents one of the inclusion criteria. Therefore, both patients at risk of malnutrition and patients who are malnourished are eligible for enrollment when the other study criteria are fulfilled. The MNA-SF will be administered by trained study personnel through a structured interview with the patient and, when appropriate, with the caregiver. The final item will be based on measured anthropometric data whenever available. To ensure consistency across centers, investigators will receive specific training on administration and scoring according to standard MNA-SF criteria.

		Score
1	**Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?**	
	• Severe decrease in food intake	0
	• Moderate decrease in food intake	1
	• No decrease in food intake	2
2	**Weight loss during the last 3 months**	
	• Weight loss > 3 kg (6.6 lbs)	0
	• Does not know	1
	• Weight loss between 1 and 3 kg (2.2–6.6 lbs)	2
	• No weight loss	3
3	**Mobility**	
	• Bed or chair bound	0
	• Able to get out of bed/chair but does not go out	1
	• Goes out	2
4	**Has suffered psychological stress or acute disease in the past 3 months?**	
	• Yes	0
	• No	2
5	**Neuropsychological problems**	
	• Severe dementia or depression	0
	• Mild dementia	1
	• No psychological problems	2
6 BMI	**Body Mass Index (BMI) or Calf Circumference (CC)**	
	• BMI < 19 kg/m² or CC < 31 cm	0
	• BMI 19 to < 21 kg/m² or CC 31 to < 35 cm	1
	• BMI 21 to < 23 kg/m² or CC 33 to < 35 cm	2
	• BMI ≥ 23 kg/m² or CC ≥ 35 cm	3

7.3 SARC-F

The SARC-F is a simple, rapid screening tool developed to identify individuals at risk of sarcopenia, particularly in older populations and clinical settings such as cardiovascular disease and pre-procedural assessment. It consists of five self-reported items evaluating key domains of muscle function: strength, assistance in walking, rising from a chair, climbing stairs, and history of falls. Each component is scored from 0 (no difficulty) to 2 (severe difficulty or inability), yielding a total score ranging from 0 to 10. A score ≥4 is commonly used as a threshold to indicate a high risk of sarcopenia and the need for further diagnostic evaluation. The SARC-F is widely used because of its ease of administration, requiring no equipment or physical testing, and its applicability across different healthcare settings. Although it has relatively low sensitivity, it demonstrates good specificity for identifying individuals with clinically relevant sarcopenia and predicting adverse outcomes such as functional decline, hospitalization, and mortality. For this reason, international guidelines, including those from the European Working Group on Sarcopenia in Older People, recommend SARC-F as an initial case-finding tool, to be followed by objective measures of muscle strength and mass when positive [17].

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds (≈ 4,5 Kg, ndr)?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1 - 3 falls = 1 4 or more falls = 2

7.4 Bioimpedence analysis

Bioimpedance analysis has been used in clinical applications since the 1980s, and nowadays it is one of the most widely used tools for investigating body composition, universally accepted as an essential element in the assessment of an individual's health status [1]. It is currently the most effective and reliable methodology for estimating body composition and fluid status in the body. Its use has increased significantly over the past decade

for its undoubted advantages, such as rapidity of execution, non-invasiveness, and low cost. Bioelectrical impedance analysis (BIA) scales are useful tools for assessing body composition in older adults, providing estimates of fat mass, lean body mass, and total body water in a quick and non-invasive way. They work by sending a very low, safe electrical current through the body and measuring the resistance (impedance) encountered as the current passes through different tissues; lean tissue, which contains more water, conducts electricity better than fat tissue. In elderly populations, this information can be particularly valuable for monitoring changes related to aging, such as sarcopenia (loss of muscle mass), dehydration, or increased fat accumulation. Regular use can help guide nutritional and clinical interventions, supporting better management of health and functional status [18].

7.5 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a validated, disease-specific, self-administered instrument developed to assess symptoms, physical limitation, social limitation, and quality of life in patients with heart failure and related cardiovascular conditions [19]. In the IRON-TAVI trial, the KCCQ is used to evaluate patient-reported health status and to capture changes over time after the study intervention and TAVI. The KCCQ explores the patient's perception of disease burden across multiple domains, including symptom frequency, symptom burden, physical limitation, quality of life, and social limitation. Domain scores are standardized on a 0-to-100 scale, with higher values indicating better health status, lower symptom burden, and less functional limitation. A summary score and, when appropriate, an overall summary score may be derived from the relevant domains according to standard scoring methods. In the IRON-TAVI trial, the KCCQ will be administered by trained study personnel according to a standardized procedure. The questionnaire may be self-completed by the patient or interviewer-administered when necessary because of frailty, visual impairment, or other practical limitations. All centers will be instructed to use the same version and scoring approach in order to ensure consistency across the study. The KCCQ is included among the study instruments for quality-of-life assessment and will be used to evaluate the effect of the intervention on patient-perceived symptoms and functional status during follow-up.

7.6 EuroQol 5-Dimension 5-Level (EQ-5D-5L)

The EuroQol 5-Dimension 5-Level (EQ-5D-5L) is a standardized, generic instrument used to assess health-related quality of life. It is widely adopted in clinical research and allows a global evaluation of the patient's perceived health status across different dimensions of daily life [20]. In the IRON-TAVI trial, the EQ-5D-5L is used to assess changes in overall quality of life during follow-up. The EQ-5D-5L evaluates 5 health domains:

i) mobility,

ii) self-care,

iii) usual activities,

iv) pain/discomfort,

v) anxiety/depression.

For each domain, the patient selects 1 of 5 levels of severity, ranging from no problems to extreme problems. The combination of responses defines a specific health state, which can be converted into an index value according to standard value sets. In addition, the EQ-5D-5L includes a visual analogue scale (EQ-VAS), in which the patient rates his or her overall health on a scale from 0 to 100, with higher values indicating better perceived health status. In the IRON-TAVI trial, the EQ-5D-5L will be administered by trained study personnel according to a standardized procedure. The questionnaire may be self-completed by the patient or interviewer-administered when necessary because of frailty, visual impairment, or other practical limitations. All centers will use the same version and scoring approach in order to ensure consistency across the study.

The EQ-5D-5L is included among the study instruments for quality-of-life assessment and will be used to evaluate the effect of the intervention on global health status during follow-up.

7.7 General definition of clinical endpoints

Unless otherwise specified, clinical endpoints will be defined and adjudicated according to the Valve Academic Research Consortium-3 (VARC-3) consensus document, whenever applicable. This approach is intended to ensure standardized endpoint classification and consistency with contemporary studies in patients undergoing transcatheter aortic valve implantation (TAVI). Clinical events will be collected by study investigators and source documentation will be obtained whenever available. Final endpoint classification will be performed by the Clinical Event Committee according to the prespecified definitions and adjudication rules. In case of endpoints not fully covered by VARC-3, or for study-specific endpoints related to the multidomain intervention, the definitions prespecified in the present protocol and in the adjudication charter will apply [21, 22].

7.7.1 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

7.7.2 Stroke

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

7.7.3 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

7.7.4 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.

7.7.5 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 STATISTICAL ANALYSIS

A detailed Statistical Analysis Plan (SAP) will be finalized before database lock and before any unblinded analysis. The SAP will prespecify in greater detail all statistical methods, derivation rules, handling of protocol deviations, censoring rules, management of missing data, sensitivity analyses, and presentation formats. All statistical analyses will be performed by independent statisticians using validated statistical software. Baseline characteristics will be summarized by randomized group using descriptive statistics only. Continuous variables will be presented as mean ± standard deviation or median with interquartile range, as appropriate according to their distribution. Categorical variables will be summarized as counts and percentages. No formal hypothesis testing will be performed for baseline comparisons. All tests will be two-sided, and a p value lower than 0.05 will be considered statistically significant unless otherwise specified. Effect estimates will be reported with 95% confidence intervals. The primary analysis population will be the intention-to-treat population, defined as all randomized patients analyzed according to the treatment group assigned at randomization, irrespective of actual treatment received, adherence to the intervention, or protocol deviations. This population will be used for the primary efficacy analysis and for the main secondary efficacy analyses. A supportive per-protocol population will also be defined and will exclude patients with major protocol deviations considered relevant for interpretation of treatment effect, according to criteria prespecified in the SAP. Per-protocol analyses will be considered supportive. Safety analyses will include all randomized patients with available post-randomization safety information and will primarily be descriptive. The primary efficacy endpoint is the 1-year cumulative occurrence of all-cause death, stroke, or hospital readmission for cardiovascular cause. The primary efficacy analysis will compare the two randomized groups using a time-to-first-event approach in the intention-to-treat population. Event-free survival curves will be estimated using the Kaplan-Meier method and compared by means of the log-rank test. The treatment effect will be estimated using a Cox proportional-hazards model and expressed as hazard ratio with 95% confidence interval. The main model will include treatment group as the primary independent variable. A supportive adjusted analysis may additionally include clinically relevant baseline covariates and randomization stratification factors, as prespecified in the SAP. Patients without a primary endpoint event will be censored at the date of the last available follow-up information. The proportional hazards assumption will be assessed using standard graphical and model-based methods. If relevant violations are detected, alternative time-to-event approaches will be prespecified in the SAP and presented as supportive analyses. Secondary time-to-event efficacy endpoints, including all-cause death, cardiovascular death, myocardial infarction, stroke, hospital readmission for heart failure, hospital readmission for cardiovascular cause, and hospital readmission for any cause, will be analyzed using methods analogous to those applied to the primary endpoint. These analyses will be interpreted as supportive or exploratory, unless

otherwise specified. For each endpoint, effect estimates will be reported as hazard ratios with 95% confidence intervals. If clinically relevant competing risks are identified for selected endpoints, supportive competing-risk analyses may be performed as prespecified in the SAP. Repeated continuous outcomes, including Short Physical Performance Battery (SPPB), Mini Nutritional Assessment Short Form (MNA-SF), Kansas City Cardiomyopathy Questionnaire (KCCQ), EuroQol 5-Dimension 5-Level (EQ-5D-5L), and related quality-of-life measures, will be analyzed using linear mixed-effects models for repeated measures. These models will include treatment group, visit, treatment-by-visit interaction, and baseline value of the corresponding outcome. Additional prespecified covariates, including relevant baseline clinical characteristics and stratification factors, may be incorporated when appropriate. A random patient-level intercept will be used to account for within-subject correlation over time, and the covariance structure for repeated measurements will be selected according to statistical and clinical appropriateness, as defined in the SAP. Treatment effects will be presented as adjusted between-group differences at prespecified follow-up time points, together with 95% confidence intervals. This likelihood-based framework allows use of all available longitudinal data and is consistent with the methodological approach adopted in recent multidomain intervention trials with repeated patient-reported or functional outcomes. Categorical secondary outcomes will be analyzed using chi-square tests, Fisher's exact tests, or generalized linear models, as appropriate. If responder thresholds are prespecified for selected functional or quality-of-life endpoints, responder analyses may be performed using generalized linear models with appropriate link and variance functions, as detailed in the SAP. In view of the number and heterogeneity of secondary endpoints, these analyses will mainly be considered supportive or exploratory, and their interpretation will be made with appropriate caution. Formal multiplicity adjustment for secondary outcomes may be adopted only if prespecified in the SAP. Safety analyses will include adverse events related to exercise training, adverse events related to dietary supplementation, worsening renal function, falls, trauma, bleeding events, temporary interruption of the intervention, incomplete adherence, and permanent discontinuation of one or more study intervention components. Safety data will be summarized descriptively by randomized group, reporting the number and proportion of patients experiencing at least one event, as well as the total number of events when appropriate. Time-to-first safety event analyses may also be performed for selected endpoints. No formal hypothesis-testing hierarchy is planned for safety outcomes, which will primarily be interpreted from a clinical perspective. Every effort will be made to minimize missing data through standardized follow-up procedures, phone contacts, review of medical records, and contact with relatives or caregivers when appropriate. For time-to-event analyses, patients with incomplete follow-up will be censored at the date of last known information. For repeated continuous outcomes, mixed-effects models will be preferred because they appropriately handle data assumed to be missing at random under likelihood-based estimation. If the extent or pattern of missing data is considered potentially influential, additional sensitivity

analyses may be performed, including multiple imputation strategies for selected outcomes, as prespecified in the SAP. Reasons for missingness, discontinuation, and withdrawal will be summarized by treatment group. Prespecified subgroup analyses of the primary efficacy endpoint may be performed to explore consistency of treatment effect across clinically relevant categories, including sex, age, baseline SPPB severity, baseline MNA-SF severity, and other clinically meaningful characteristics defined before database lock. Subgroup analyses will be performed by testing treatment-by-subgroup interaction terms within Cox regression models. These analyses will be considered exploratory and interpreted cautiously. No formal interim efficacy analysis is planned. Interim safety reviews will be conducted by the Data Safety Monitoring Board according to the DSMB charter. Any unblinded review performed by the DSMB will remain independent from the investigators and from the statisticians responsible for the final efficacy analyses. Formal control of type I error will be ensured for the primary efficacy endpoint. If a hierarchical testing strategy for selected secondary outcomes is adopted, it will be fully prespecified in the SAP before database lock.

8.1 Determination of sample size

The primary efficacy endpoint of the IRON-TAVI trial is the 1-year cumulative occurrence of all-cause death, stroke, or hospital readmission for cardiovascular cause. Based on previous studies enrolling patients with aortic stenosis and reduced physical performance and/or poor nutritional status, the expected occurrence of the primary endpoint in the control group is assumed to be 35%. The trial is designed to detect a 35% relative risk reduction in the experimental group, corresponding to an absolute reduction from 35.0% to 22.75%. Assuming a two-sided alpha level of 0.05 and a power of 80%, 214 patients per group are required, for a total of 428 patients. To account for attrition, incomplete follow-up, and possible loss of information, the final sample size is increased to 450 patients.

Summary of the statistical analysis framework of the IRON-TAVI trial

Item	Planned approach
Primary analysis population	Intention-to-treat population
Supportive population	Per-protocol population
Safety population	All randomized patients with available post-randomization safety data
Primary endpoint	1-year cumulative occurrence of all-cause death, stroke, or hospital readmission for cardiovascular cause
Primary endpoint analysis	Kaplan-Meier estimates, log-rank test, Cox proportional-hazards model
Primary treatment effect measure	Hazard ratio with 95% confidence interval
Secondary time-to-event endpoints	Cox proportional-hazards models and supportive time-to-event methods
Repeated continuous outcomes	Linear mixed-effects models for repeated measures
Categorical outcomes	Chi-square test, Fisher's exact test, or generalized linear models, as appropriate
Safety analyses	Primarily descriptive, by randomized group
Missing time-to-event data	Censoring at last known follow-up
Missing repeated continuous data	Likelihood-based mixed models; sensitivity analyses if needed
Subgroup analyses	Exploratory, based on treatment-by-subgroup interaction terms
Interim efficacy analysis	Not planned
Interim safety review	Performed by the DSMB according to charter
Type I error control	Formal for the primary endpoint; secondary hierarchy only if prespecified in the SAP
Planned sample size	450 patients

9 ETHICAL AND REGULATORY STANDARDS

9.1 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.

9.2 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.

9.3 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.

9.4 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.

9.5 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.

10 ADMINISTRATIVE RULES

10.1 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.

10.2 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.

10.3 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.

11 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.

12 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.

13 STUDY ADMINISTRATIVE INFORMATION

13.1 ADDRESS LIST

13.1.1 Study Committees

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

13.1.2 Sponsor

Azienda Ospedaliero Universitaria di Ferrara

13.1.3 Principal Investigator

Elisabetta Tonet

13.1.4 Academic Research Organization

Cardiology Unit, University Hospital of Ferrara

Via Aldo Moro 8, Cona (FE), Italy

13.2 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.

13.3 FUNDING AND SUPPORT

The IRON-TAVI trial received funding from the Italian Ministry of Health within the framework of the “Ricerca Finalizzata 2024” program (Project code: GR-2024-12377447). The funding source had no role in study design and will have no role in data collection, data analysis, data interpretation, or manuscript writing.

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