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Original article

Telematic intervention on frailty in patients undergoing TAVI. Design of the TELE-FRAIL TAVI clinical trial

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ABSTRACT

Introduction and objectives: Although transcatheter aortic valve implantation (TAVI) is the first-line therapy for aortic stenosis (AS), its benefit could be lower (or even disappear) in frail patients. Physical exercise and nutritional support programs are recommended to address frailty. Data on the application of telemedicine strategies in this context is scarce. The objective of this study is to analyze, in older patients with AS undergoing TAVI, the effect of a telematic intervention on the reversal of frailty vs standard of care.

Methods: We will be conducting a randomized multicenter study including patients aged ≥ 75 years with severe AS (mean aortic gradient > 40 mmHg, or aortic valve area < 0.8 8 cm^2 on echocardiogram) with baseline frailty criteria (Short Physical Performance Battery [SPPB] < 10 and FRAIL scale ≥ 3) undergoing TAVI. Prior to discharge, patients will be randomized to *a)* a telematic intervention within the first 3 months (nutritional support plus supervised physical exercise plus health education); or *b)* standard of care. The primary endpoint will be the percentage of patients with frailty reversal (SPPB ≥ 10) at 3 months. The estimated sample size is 206 patients (103 in each arm).

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Conclusions: The hypothesis of this study is that telematic intervention will allow a higher percentage of frailty reversal at 3 months vs standard of care after TAVI. The results of this study may provide novel information on this approach to frail patients with AS undergoing TAVI.
ClinicalTrials.gov registered trial (NCT06742970).

Keywords: Aortic stenosis. TAVI. Telemedicine. Frailty.

Intervención telemática sobre la fragilidad en pacientes tratados con TAVI. Diseño del ensayo clínico TELE-FRAIL TAVI

RESUMEN

Introducción y objetivos: El implante percutáneo de válvula aórtica (TAVI) constituye un tratamiento de primera línea en la estenosis aórtica (EAo), aunque en pacientes frágiles su beneficio podría ser menor. Para el abordaje de la fragilidad se recomiendan los programas de ejercicio físico y soporte nutricional. No existe experiencia sobre la aplicación de la telemedicina en este contexto. El objetivo de este estudio es analizar, en pacientes mayores con EAo tratados con TAVI, el efecto de una intervención telemática en la reversión de la fragilidad en comparación con el abordaje convencional.
Métodos: Estudio multicéntrico aleatorizado. Se incluirán pacientes ≥ 75 años con EAo grave (gradiente aórtico medio > 40 mmHg o área valvular aórtica < 0,8 cm^2 en el ecocardiograma) con criterios de fragilidad basal (*Short Physical Performance Battery* [SPPB] < 10 y escala FRAIL ≥ 3) tratados con TAVI. Los pacientes serán aleatorizados antes del alta para recibir: *a)* intervención telemática durante los primeros 3 meses (soporte nutricional + ejercicio físico tutelado + educación sanitaria) o *b)* abordaje habitual. El criterio de valoración principal será el porcentaje de pacientes con reversión de la fragilidad (SPPB ≥ 10) a los 3 meses. El tamaño muestral planteado es de 206 pacientes (103 en cada rama).
Conclusiones: La hipótesis del estudio es que una intervención telemática permitirá un mayor porcentaje de reversión de la fragilidad a los 3 meses del TAVI en comparación con el seguimiento habitual. Se espera que los resultados de este estudio aporten información novedosa para el abordaje del paciente frágil con EAo tratado con TAVI.
Ensayo registrado en ClinicalTrials.gov (NCT06742970).

Palabras clave: Estenosis aórtica. TAVI. Telemedicina. Fragilidad.

Abbreviations

AS: aortic stenosis. **SPPB:** Short Physical Performance Battery. **TAVI:** transcatheter aortic valve implantation.

INTRODUCTION

Degenerative aortic stenosis (AS) is the most common valvular heart disease in Western countries, largely due to the increase in life expectancy and the progressive aging of the population. Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of AS, with documented efficacy in inoperable patients,[1] high surgical risk patients,[2] and more recently, in patients with intermediate or low surgical risk.[3,4] This growing body of evidence has led to a progressive increase in the number of TAVIs performed each year,[5] creating a need within health care systems to adapt to this demand and optimize care pathways and hospital admissions.[6]

AS is an age-related condition. The presence of frailty, comorbidity, and other geriatric syndromes is closely associated with the rate of complications, need for hospital readmissions, and mortality in both conservatively treated patients[7] and those undergoing surgery[8] or TAVI.[9] Both frailty and comorbidity burden are also associated with a higher rate of procedureal complications,[10] despite the fact that technological advancements have made TAVI an increasingly less invasive procedure. Furthermore, prior data suggest that patients with a higher comorbidity burden face higher rates of readmissions and non-cardiac mortality, which may limit or even negate the benefits of TAVI in some individuals.[11] Therefore, optimizing patient selection to avoid procedural futility remains one of the most pressing clinical challenges.

On the other hand, the frailty phenotype is defined as a potentially reversible state of vulnerability to external stressors.[12,13] In patients with cardiovascular disease, a significant portion of this frailty is attributable to the heart condition *per se* and is, therefore, potentially reversible through specific treatment. However, in patients with a higher comorbidity burden, it may be difficult to determine what proportion of this frailty is associated with other underlying health conditions. It has been proposed that treating patients with incipient frailty requires a comprehensive approach to achieve reversal,[14] including physical exercise, adequate nutrition, and tight control of comorbidities, which can accelerate the development of frailty. Some publications have shown that exercise programs can partially reverse frailty in various cardiovascular settings, including patients with AS.[15-17] However, implementing these strategies in the routine clinical practice faces major obstacles, due to the cost associated with including this growing patient population in cardiac rehabilitation programs and the difficulty of achieving sustained adherence. Previous experiences show low adherence to hospital-based exercise programs (around 30%) even in controlled clinical trial settings.[18]

Telemedicine offers potentially significant advantages in the management of older patients with frailty and cardiovascular disease, as it may enable adequate follow-up by overcoming logistical barriers (need for transportation, suboptimal adherence), which are particularly relevant in this context. Various

telemedicine tools have demonstrated their usefulness in improving prognosis in patients with heart failure,[19] thus allowing for early detection of decompensation and prevention of hospitalizations and other complications. However, to this date, there is no experience on the application of telemedicine to frail patients with AS undergoing TAVI.

For these reasons, the main endpoint of the TELEFRAIL TAVI clinical trial is to analyze, in patients with AS undergoing TAVI, the effect of a comprehensive telematic intervention on frailty reversal 3 months after the intervention vs standard care.

METHODS

Study design

We conducted a prospective, multicenter, randomized (1:1) clinical trial to compare a comprehensive telematic intervention targeting frailty vs standard post-discharge care in patients ≥ 75 years with AS and frailty criteria undergoing TAVI. The study is promoted by the Section of Geriatric Cardiology of the Spanish Society of Cardiology and will be conducted in 20 Spanish hospitals, with participation from clinical and interventional cardiologists, geriatricians, and other specialists experienced in the management of these patients, as well as trained nursing staff. The trial is registered at ClinicalTrials.gov (NCT06742970).

Study population

Eligible patients must meet the following inclusion criteria: *a)* severe AS, defined by a mean aortic gradient > 40 mmHg or an aortic valve area < 0.8 cm^2 on echocardiography; *b)* age ≥ 75 years; *c)* undergoing TAVI during hospitalization; and *d)* meeting baseline (preoperative) frailty criteria defined by a Short Physical Performance Battery (SPPB) score < 10[20] and a (Fatigue, Resistance, Ambulation, Illnesses, Loss of weight) FRAIL score ≥ 3.[21]

Exclusion criteria include *a)* refusal to participate; *b)* inability to complete geriatric assessments or follow study procedures; *c)* inability to understand or sign informed consent forms; and *d)* life expectancy < 12 months.

Beyond defined criteria, patient inclusion and derived procedures must be deemed reasonable by the responsible medical team. If complications occurred during hospitalization, they must be reasonably resolved prior to inclusion.

Treatment protocol

Prior to performing TAVI, baseline geriatric assessment will be conducted via interview with the patient, family, or caregivers by multidisciplinary trained personnel at participant centers. We'll assess functional capacity for basic activities of daily living using the Barthel Index,[22] an ordinal scale ranging from 0 to 100. This scale categorizes dependence into total (0–20), severe (21–40), moderate (41–60), mild (61–90), and independent (> 90). Instrumental activities will be assessed using the Lawton and Brody scale.[23] Moreover, we'll evaluate cognitive status with the Pfeiffer Test[24] and Mini Mental State Examination (MMSE),[25] and frailty using the SPPB[20] including *a)* balance in 3 positions (feet together, semi-tandem, tandem); *b)* gait speed (4 m); and *c)* 5 chair stands. The total SPPB score goes from 0 to 12, with scores < 10 indicating increased risk of disability and falls. Furthermore, we'll assess frailty using the FRAIL scale,[21] the Clinical Frailty Scale,[26] and the Essential Frailty Toolset[8] including *a)* 5 chair stands; *b)* MMSE;[25] *c)* hemoglobin values; and *d)* albumin levels. Additionally, we'll assess comorbidity using the Charlson Comorbidity Index[27] (maximum score, 37) and record the number of chronic prescription drugs prior to admission. Finally, we'll assess nutritional using the Mini Nutritional Assessment-Short Form (MNA-SF)[28] (scores < 11 indicate malnutrition risk). Quality of life will be evaluated using the EQ-5D-5L questionnaire.[29]

Patients meeting frailty criteria and consenting to participate will be randomized before hospital discharge (post-TAVI) to 2 treatment arms: *a)* comprehensive telematic intervention (nutrition + supervised exercise + health education) within the first 90 days, or *b)* standard post-discharge care. Patients will be randomized using an online computer-generated 1:1 scheme, with concealed allocation. In-hospital medical therapy will follow clinical practice guidelines and the treating team's judgment.

Frailty intervention

We will perform the intervention to allocated patients within the 90 days following discharge via a specialized central telematic platform. Afterwards, expert health care professionals in nutritional support and adapted physical exercise will conduct videocalls on week 1, day 15, and every 2 weeks within the first 3 months.

For physical exercise, we'll use an adaptation of the VIVI FRAIL program.[30] On week 1, we'll be using protocol A, moving to protocol B up to day 30 after discharge depending on good clinical tolerance, eventually moving to protocol C during months 2 and 3. The entire process will be monitored through periodic videocalls by specialists in physical exercise for elderly patients. In addition, patients and their families will have access to a phone number to resolve doubts, which will be available during working hours from Monday through Friday throughout the entire process.

Regarding nutritional support, patients allocated to the frailty intervention group will receive nutritional information best suited to each individual profile after hospital discharge. The research team will provide nutritional supplements for 3 months after discharge. Patients will receive nutritional supplementation with a hypercaloric and hyperproteic formula. Nutritional supplements will be taken once a day after completing the corresponding exercise regimen during that period (3 months).

Health education will consist of complementing the information received on nutrition and exercise during successive videocalls within the first 3 months and resolving any related questions. Moreover, we'll provide information to optimize treatment adherence and control cardiovascular risk factors.

Study endpoints

The primary endpoint will be the percentage of patients whose frailty is reversed, as measured by SPPB[20] (meaning they achieve an SPPB score of ≥ 10) 3 months after discharge. Staff from participant centers blinded to the allocated treatment group will be conducting this assessment (figure 1).

The following will be analyzed as secondary endpoints:

- Number of days alive and out of hospital 1 year[31] after TAVI.
- Need for readmission (cardiac or non-cardiac) at 3 months and 1 year.
- All-cause and cardiovascular mortality rates at 3 months and 1 year.

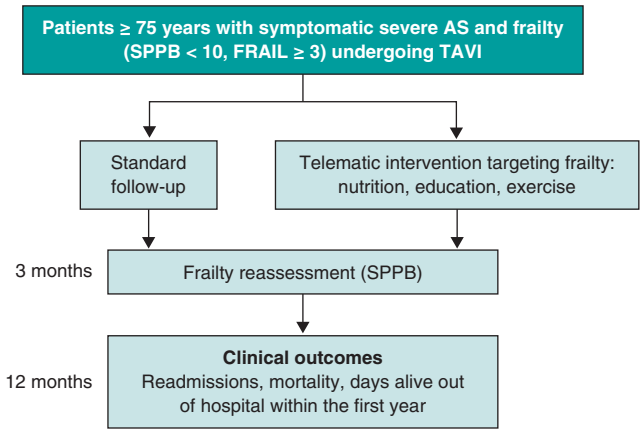

Figure 1. TELE-FRAIL TAVI study design. AS, aortic stenosis; SPPB, Short Physical Performance Battery; TAVI, transcatheter aortic valve implantation.

- Rate of cardiovascular events (MI, stroke, revascularization) at 1 year.
- Proportion of robust patients (SPPB >10) at 1 year.
- Disability (Barthel Index[22]) at 3 months and 1 year.
- Nutritional risk (MNA-SF[28]) at 3 months and 1 year.
- Quality of life (EQ-5D-5L[29]) at 3 months and 1 year.

Geriatric assessment during follow-up

A trained staff member from the participant centers will conduct the geriatric assessment in person. This staff will be blinded to the allocated treatment group. Three months and 1 year after TAVI, we'll re-evaluate functional capacity (Barthel Index), instrumental activities of daily living (Lawton-Brody Index), nutritional risk (MNA-SF), cognitive ability (Pfeiffer test), quality of life (EQ-5D-5L), and frailty using the FRAIL, Clinical Frailty Scale, SPPB, and Essential Frailty Toolset scales. Clinical follow-up includes an in-person visit at 3 months and 1 year.

Study committees

This project is an independent clinical trial, with no industry funding. A steering committee will be responsible for overseeing the scientific and operational aspects of the study. While patients and researchers won't be blinded to the treatment group allocation, a blinded event adjudication committee will evaluate clinical events to prevent bias. Similarly, a data safety monitoring board will be responsible for making relevant recommendations to the steering committee regarding the endpoints, as well as any potential observations related to patient safety.

Statistical analysis and sample size

Previous data from elderly patients with severe AS and frailty criteria undergoing TAVI show an approximate 50% proportion of frailty reversal after TAVI. Assuming an estimated 70% frailty reversal in the group allocated to the post-discharge telemedicine intervention, with 80% statistical power and a two-sided alpha error of 0.05, and accounting for a 10% loss to follow-up, the calculated sample size is 206 patients (103 in each group). A multicenter approach is necessary to achieve this planned sample size.

All statistical comparisons will follow the intention-to-treat principle. Results will be expressed as frequency and percentage or as median and standard deviation, as appropriate. Inter-group comparisons will be drawn using Fisher's exact test. Patient follow-up will be censored at the time of death or at the end of the study. Primary endpoints will be compared between the 2 groups using a logistic regression model, considering frailty reversal as the dependent variable, the intervention as a fixed independent variable, and other covariates with a significant association with exposure in the final statistical model. In addition to secondary endpoints, the effect of the intervention on clinical events will be described using the Kaplan-Meier method, and Cox regression will be used for its evaluation. Hazard ratios and their 95% confidence intervals will be calculated. For all analyses, a two-sided $P < .05$ will be considered statistically significant. If significant differences are observed in the distribution of covariates between the 2 groups (control vs intervention), all variables with a significantly different distribution between the 2 groups, in addition to the allocated treatment group, will be included in the adjusted analysis. Prespecified subgroup analyses will be performed based on sex and comorbidity burden (Charlson Comorbidity Index).

Ethical aspects

Both participants and their families will receive detailed information about the potential risks and benefits of participating in the study. Both the study protocol and the informed consent form have been evaluated by the reference ethics committee. Participants will have the opportunity to carefully read the consent form and ask questions before signing it. All participants must sign the informed consent form prior to being included in the study. A copy of such form will be provided to participants. The rights and benefits of participants will be protected, with an emphasis that the quality of medical care will not be negatively impacted if they refuse to participate in the study.

DISCUSSION

Despite TAVI has become the treatment of choice in most elderly patients with AS, avoiding futility in patients with a higher burden of comorbidity, frailty, and disability remains clinically challenging. Therefore, a considerable percentage of elderly AS patients present with frailty, partly due to their heart disease (potentially reversible with specific treatment), and partly due to other existing comorbidities. In patients with a high comorbidity burden, isolated treatment of AS may not provide clinical benefit in the absence of other additional measures.[11] A detailed understanding of each patient's profile is essential for appropriate therapeutic planning both for AS and for the overall health status once the valvular heart disease has been corrected.

Frailty is considered an intermediate state in the transition toward disability that is potentially reversible, especially in its early stages.[13] A holistic, multidisciplinary approach supported by physical exercise, proper nutrition, and tight control of underlying disease is essential.[14] Some physical activity programs have partially reversed frailty in various cardiovascular contexts, including patients with AS.[15-17] However, implementing these strategies in the routine clinical practice faces substantial challenges due to cost and the difficulty in ensuring sustained patient adherence.[18] The TELE-FRAIL TAVI clinical trial aims to assess the potential impact of a comprehensive intervention on frailty reversal and prognosis in frail elderly patients undergoing TAVI. The telematic design of the intervention is expected to facilitate greater adherence to exercise and nutrition recommendations, thus contributing to frailty reversal along with AS correction via TAVI. The study design should allow

determination of the percentage of patients in whom frailty is reversed with this combined strategy vs conventional TAVI follow-up. Furthermore, it should identify the clinical and geriatric profile of patients in whom the strategy fails, indicating a high likelihood of procedural futility.

CONCLUSIONS

The results of the TELE-FRAIL TAVI clinical trial are expected to shed light on the optimal management of frail elderly patients with AS undergoing TAVI. Optimizing treatment and prognosis for these complex patients could have significant clinical, financial, and social implications.

FUNDING

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ETHICAL CONSIDERATIONS

Both the study protocol and the informed consent form were reviewed and approved by the relevant ethics committee. All participants must sign the informed consent form prior to being included in the study.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Not used.

AUTHORS' CONTRIBUTIONS

E. Bernal-Labrador, R. Romaguera, F. Formiga, and A. Ariza-Solé contributed to the study conception and manuscript drafting. S. García-Blas, A. Regueiro, V. Serra, H. Tizón-Marcos, L. Asmarats, V. Agudelo, C. Scardino, J.M. Casanova-Sandoval, T. Rodríguez-Gabella, C. Jiménez-Méndez, A. Pérez-Rivera, C. Robles-Gamboa, A. Ayesta, P. Díez-Villanueva, S. Raposeiras-Roubín, I. Amat-Santos, A. Esteve-Pastor, G. Veiga-Fernández, M. Anguita, D. Martí-Sánchez, N. Martínez-Velilla, L. Cortés, E. Calvo-Barriuso, and S. Asimbaya contributed to critical manuscript revision.

CONFLICTS OF INTEREST

R. Romaguera is Associate Editor of *REC: Interventional Cardiology*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed. The remaining authors declared no conflicts of interest whatsoever.

WHAT IS KNOWN ABOUT THE TOPIC?

- Although transcatheter aortic valve implantation (TAVI) is a first-line therapy for aortic stenosis (AS), its benefit may be significantly lower in frail patients with comorbidities.
- Although a comprehensive approach (physical exercise, appropriate nutrition, comorbidity control) is recommended to reverse frailty, its implementation in clinical practice faces major challenges.
- Telemedicine could provide adequate follow-up and improved adherence to such programs in frail elderly patients.
- There is no experience with telemedicine applied to frail patients undergoing TAVI.

WHAT DOES THIS STUDY ADD?

- The TELE-FRAIL TAVI clinical trial will analyze, in patients with AS undergoing TAVI, the effect of a comprehensive telematic intervention on frailty reversal 3 months after TAVI vs conventional management.
- The study design should reveal the percentage of patients achieving frailty reversal with the combined strategy vs standard follow-up, and the clinical profile of patients in whom the strategy fails, and for whom TAVI may be futile.

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