Rational and design of the Baseline Interatrial block and Transcatheter aortic valve implantation (BIT) registry☆

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ABSTRACT

Background: Aortic stenosis (AS) is currently the most frequent heart valve disease. Symptomatic severe AS has a poor prognosis and transcatheter aortic valve implantation (TAVI) is becoming the therapy of choice in these patients. Changes in the conduction tissue after the procedure constitute one of the main limitations of TAVI, with a frequent need for a definitive pacemaker. Interatrial block (IAB) is defined as a prolonged P-wave duration and is related with atrial fibrosis. The presence of IAB could be a marker of conduction tissue abnormalities at other levels. No study has specifically analyzed the role of IAB as a predictor of the need for permanent pacemaker in patients with AS undergoing TAVI.

Methods: The Baseline Interatrial block and Transcatheter aortic valve implantation (BIT) registry will be performed in approximately 3000 patients with severe AS treated with TAVI. A centralized analysis of baseline ECGs will study the presence and type of IAB and other ECG data (rhythm, P-wave duration, PR and QRS intervals/intraventricular conduction disorders). Clinical follow-up will be carried out by local researchers. The primary endpoint will be the requirement of permanent pacemaker during post-TAVI hospitalization. As secondary objectives, the incidence of new onset AF, stroke, or mortality during follow-up will be analyzed. Secondary endpoints will include the incidence of new onset AF, stroke, or mortality during follow-up.

Conclusion: The BIT registry will study, for the first time, the influence of previous IAB in the need of permanent pacemaker after TAVI: This large registry will also provide information regarding the association of this and other ECG parameters with prognosis.

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Introduction

Aortic stenosis (AS) is currently the most frequent heart valve disease in developed countries [1]. Patients with symptomatic severe AS have a poor prognosis [2,3] and a clear indication of aortic valve intervention. Surgical aortic valve replacement used to be the treatment of choice, but the emergence of transcatheter aortic valve implantation (TAVI) has brought a real revolution in the management of these patients [4–6].

Changes in the conduction tissue after the procedure constitutes one of the main limitations of TAVI, generating the need for a definitive pacemaker in a non-negligible percentage of patients [7]. Some predictors for permanent pacemaker implantation have been described [8,9], but information on this matter is still insufficient. In fact, the appearance of conduction disorders and the difficulties in their prediction are one of the main limitations for the early discharge of these patients.

Several authors have suggested that interatrial block (IAB) could be a precursor of atrial fibrillation (AF) in different clinical scenarios [10–12], including patients undergoing TAVI [13]. IAB is defined as a prolonged P-wave duration (≥120 ms). In partial IAB the P-wave is positive in the inferior leads while in advanced IAB the P-wave has a biphasic (+-) pattern in the inferior leads. IAB is thought to represent an interatrial conduction delay (partial) or blockage (advanced) in the Bachmann region. When the stimulus is completely blocked in the upper part of the atrium (as in advanced BIA), a good part of the left atrium is stimulated in a caudocranial direction, which is reflected in the electrocardiogram as a biphasic P wave in the inferior leads. As in the case of AF, atrial fibrosis has been suggested as the potential mechanism associated with these alterations in interatrial conduction [14]. Fibrosis, arteriosclerosis, and AS are frequently associated with aging. This is also the case in IAB [15–17]. Therefore, the presence of IAB in the ECG could be considered a marker of conduction tissue abnormalities at other levels. No study has specifically analyzed the role of IAB as a predictor of the need for permanent pacemaker in patients with AS undergoing TAVI.

Methods

Study population

The Baseline Interatrial block and Transcatheter aortic valve implantation (BIT) registry will be performed in approximately 3000 patients with severe AS treated with TAVI in 8 Spanish academic centers. Inclusion criteria will be: 1) recent pre-implant ECG performed in the previous 24 h (all patients, also those without sinus rhythm will be included) 2) TAVI. The only exclusion criteria will be unavailable ECG in the 24 h before TAVI or ineligible ECG.

Data collection

Data will be collected prospectively by trained personnel using case report forms. Demographic data, baseline clinical characteristics, and electrocardiographic data will be obtained, as well as data from echocardiography, laboratory results, and angiographic parameters. Comorbidity will be quantified by the Charlson index. Data related to the procedure and in-hospital evolution will also be collected. These will include requirement for permanent pacemaker, invasive procedures, and in-hospital complications (bleeding events, need for transfusions, need for surgery, infectious complications requiring antibiotic therapy, infarction, arrhythmic complications, and in-hospital mortality). Bleeding events will be characterized using the International Classification of Disease, 10th Version (ICD-10) administrative hospital discharge data.

ECG and ECG analysis

A standard 12-lead electrocardiogram recording for each participant will be digitalized (scanned at 300 DPI minimum). A standardized protocol and settings (25 mm/s and 10 mm = 1 mV) will be used to record all the electrocardiograms. P-wave duration and the presence of IAB will be manually measured and assessed. To measure P-wave duration we will analyze the digitalized ECG images using the GeoGebra 4.2 software. The ECG image will be amplified up to 20 times its original size to define the interval between the earliest and the latest detection of atrial depolarization in the frontal leads, defined as a positive or negative deflection, respectively, that deviates from the base line before the QRS complex. The software allows to manually draw lines on the ECG and provides the distance between two points, which will be converted to milliseconds (ms).

Blinded ECG analysis will be performed in the core lab of the *Fundación Investigación Cardiovascular/Programa-ICCC Cardiovascular, Institut de Recerca del Hospital de la Santa Creu i Sant Pau*, Barcelona, Spain. The last ECG available before TAVI implantation will be used.

The duration of the P wave will be analyzed in at least 3 leads (ideally in 6 leads of the frontal plane). In doubtful cases the duration of the P wave will also be analyzed in precordial leads. The measurement of the P wave will be made using 2 calipers, the first of which is aligned with the first appearance of the P wave, and the second with the last final appearance of the P wave. For the definition of the presence of BIA will use, as explained previously, the criteria of Bayés de Luna et al. [10], considering partial BIA the duration of the wave P > 120 ms and complete BIA the duration of the wave P > 120 ms with biphasic morphology in lower leads.

The baseline rhythm (AF/sinus rhythm/pacemaker/others), P-wave duration, PR and QRS intervals, as well as the presence of intraventricular conduction disorders will also be analyzed.

Clinical monitoring

Clinical follow-up will be carried out by local researchers through a physical visit, review of medical records, or telephone contact with the patient, relatives or referring physician.

Study endpoints

The primary endpoint of the study will be the requirement of permanent pacemaker during post-TAVI hospitalization. Secondary endpoints will include the incidence of new onset AF, stroke, or mortality during follow-up.

Statistical analysis

Categorical variables will be expressed as n (%). Continuous variables will be expressed as mean (standard deviation), except for those non-normal distribution, in which case they will be expressed as median (interquartile range). Normality in the distribution of continuous variables will be analyzed by the Kolmogorov-Smirnov test.

The differences between categorical variables will be analyzed through the Chi-square test, with continuity correction if indicated. The differences between continuous variables will be analyzed using the Student's t-test.

For the analysis of the impact of IAB on the need to implant a permanent pacemaker after TAVI, a binary logistic regression model will be used, considering the need for permanent pacemaker as a dependent variable and those variables with significant association ($p < 0.05$) in univariable analysis, in addition to the presence of IAB. For the analysis of the impact of IAB in the combination of new onset AF, stroke, or death, a Cox regression model will be used, using this combined variable as a dependent variable and those factors with significant association ($p < 0.05$) in univariate analysis, in addition to the presence of IAB. Survival curves will be represented by the Kaplan-Meier method. Statistical packages SPSS 20 (SPSS Inc., Chicago, IL, USA) and STATA 14.0 (Stata Corp., College Station, TX, USA) will be used to carry out all statistical analysis.

Sample size calculation

There is no information on the impact of the presence of IAB on the need to implant a permanent pacemaker after TAVI. Based on previous data and assuming a rate between 15 and 20% of pacemaker implantation, the sample size proposed (around 3000 patients) guarantees a sufficient number of events for an adequate analysis of this possible association. The sample size estimation is based on the association between BIA and the requirement of permanent pacemaker during post-TAVI hospitalization and the following assumptions:

a) Incidence of permanent pacemaker implantation during post-TAVI hospitalization in patients without BIA, estimated to be around 20% (for individuals with a normal P-wave duration).

b) Effect size of the association between the presence of IAB and permanent pacemaker implantation during post-TAVI hospitalization. Little information exists about this association, thus lacking enough data to allow precise measurement of the sample size. Patients with partial IAB may present two times higher incidence of permanent pacemaker implantation during post-TAVI hospitalization than the group of individuals with a normal P-wave, and those with advanced IAB may present even a higher risk.

We expect a prevalence of sinus rhythm of 60%. With a prevalence of partial IAB of 20% and of advanced IAB of 5%, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, the inclusion of 3000 subjects will provide with enough power to detect statistically significant relative risk greater than or equal to 1.5 between the groups of partial IAB and normal P-wave, and a relative risk greater than or equal to 2 between the groups of advanced and partial IAB.

Ethical aspects

BIT is a non-interventional observational registry. The inclusion in the registry will not imply any change in clinical management. All personal information will be hidden and treated confidentially without the option of identifying patients. The provisions of current legislation in Spain and in the European Union on the protection of personal data will be complied. This registry has been approved by the ethics committee of the Germans Trias i Pujol University Hospital, Badalona, Barcelona, Spain.

Discussion

AS is the most frequent valve disease in the elderly and TAVI is becoming the therapy of choice in symptomatic patients. One of the limitations of TAVI is the damage of conduction tissue that sometimes leads to the need for permanent cardiac stimulation. This situation is variable depending on the series and the type of prosthesis implanted, although its frequency ranges between 15 and 30% and may result in prolonged hospital stay and an increased risk of complications. Although some predictors of post-TAVI conduction disorders have been described, the uncertainty about the evolution of atrioventricular conduction hinders early discharge, one of the main advantages of TAVI compared with surgical valve replacement. The presence of IAB is related with fibrosis and is a predictor of new onset AF. A small study [13] showed a slightly higher incidence of AF in patients undergoing TAVI with a previous advanced IAB. It has been suggested that aging of the conduction tissue and atrial fibrosis could constitute an anatomical substrate of IAB. In fact, the presence of IAB is more frequent in elderly patients and an association between advanced IAB and the prevalence of frailty has been described [17]. No study has specifically analyzed the association between the presence of IAB and the requirement of permanent pacemaker in patients with severe AS treated with TAVI. The description of this potential association could have clinical relevance, as it is a simple and inexpensive measurement that could contribute to a better selection of patients and the type of prosthesis to implant in this clinical scenario. Moreover, previous data support the clinical significance of conduction disturbances after aortic valve intervention [18] that are an impediment for an early discharge after TAVI [19]. The mechanisms of post-TAVI ECG changes are not completely understood [20], but a previous fibrotic conduction system might be a predisposing factor. In fact, previous ECG abnormalities have been related with a poor prognosis after TAVI, this is the case with AF, as its presence at baseline is associated with an increased mortality and stroke risk [21,22]. Also, prolonged PR interval, right and left bundle branch blocks, bifascicular block, and QRS duration >120 ms have been associated with a higher risk for pacemaker dependency after TAVI [8,9,23–28]. Moreover, the

need for a permanent pacemaker is related with a longer duration of hospitalization and higher rates of repeat hospitalization and mortality [28,29]. In spite of all the data regarding baseline ECG predictors associated to the need of permanent pacemaker, BIA has not been evaluated so far. BIA has a high prevalence among elderly patients [16] and is associated with conduction system fibrosis [30]. So, we expect that the results of the BIT registry might contribute to a better prediction of the need of permanent pacemaker after TAVI, and, thus, to improve the therapeutic management of elderly patients with severe symptomatic AS submitted to this intervention.

Limitations

A high prevalence of AF and pacemakers carriers is expected in this population. Thus, the effect of IAB on the need of permanent pacemaker implantation cannot be studied in them. This is the reason why we will study a large population. Although the exclusion of patients with non-sinus rhythm could be a possibility, we prefer to keep all patients with a recent ECG before TAVI implantation in order to study other electrocardiographic predictors of poor prognosis. Moreover, this will give us an idea of the real prevalence of previous ECG abnormalities in a large cohort of patients submitted to TAVI. All our data will come from academic hospitals in Spain and might not be extrapolated to other centers.

Conclusion

The BIT registry will study, for the first time, the influence of previous IAB in the need of permanent pacemaker after TAVI: This large registry will also provide information regarding the association of this and other ECG parameters with prognosis.

Role of the funding source

None.

Declaration of competing interest

None.

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