

STIM - TAVI

STIMulation cardiaque et TAVI : évolution des troubles conductifs atrio-ventriculaires après TAVI

Date of the protocol : October 15, 2015

English title : STIMTAVI : Evolution of Atrioventricular Conduction Disorders After TAVI

Main Investigator :

Dr IRLES Didier

Cardiology – Annecy Hospital

FRANCE

dirles@ch-annecygenevois.fr

+33 4 50 63 66 03

Scientific Committee :

French Society of Cardiology

Study Manager : Research department - Annecy Hospital

Statistics Manager :

Dr JUND Jérôme – Annecy Hospital

jjund@ch-annecygenevois.fr

+33 4 50 63 64 48

Summary

I. State of the art

II. Study Objectives

III. Criteria for judgments

IV. Population concerned

V. Investigation Method

VI. Regulatory and pharmacovigilance

VII. Collection, processing and data transfer

VIII. Nature of collected data

IX. Data analysis method

X. Research duration and number of patients included

XI. References

List of Abbreviations

ARC: Assistant (e) Clinical Research

AVB: atrioventricular block

TAVI: transcatheter aortic valve implant

A-V: atrioventricular

AAI: Pacing mode with atrial sensing and Pacing

DDD pacing mode with atrial and ventricular sensing/pacing

PM: pacemaker

CI: confidence interval

EGM: endocardial electrogram (leads of the pacemaker)

EKG: electrocardiogram

I. State of the Art:

Atrioventricular (A-V) conduction disorders are common after Transcatheter Aortic Valve Implantation (TAVI) and the average of a pacemaker implantation after TAVI is 15% to 17% (1) (2) (3) (4).

The European Society of Cardiology recommends to implant a permanent pacemaker (PM) in case of persistent high-grade A-V block (AVB) within 7 days of a TAVI procedure (class I recommendation, level of evidence C) (2).

Some conduction disturbances are transient and might not need a definitive indication for pacemaker implantation. A recent study, based on dependency of patients to pacing, estimate that in half the patients, conduction disturbances that led to the implantation of a pacemaker after TAVI procedure would have disappeared 30 days after the procedure (5).

Many studies tried to better define the indications of these devices. However, their evaluation criterias do not allow to prove these pacemakers were useful, because these studies are mainly based on the rate of implantation of pacemakers, or on the percentage of ventricular pacing. These studies may overestimate the usefulness of the pacemaker because of unnecessary ventricular pacing, or underestimate it in patients with high grade paroxysmal AVB, that could have been responsible for syncope or death (3) (4) (6) (7).

Today some pacemakers allow a better occurrence of spontaneous A-V conduction and monitor precisely the atrioventricular conduction.

The AAI SafeR® mode from Sorin® allows the pacemaker to switch from a single to a dual chamber mode in case of AVB; these switches are stored in the memories of PM as endocardial electrogram (EGM) which can be validated afterwards. The use of this algorithm could allow an accurate assessment of the persistence of high level conduction disturbances in patients implanted with a pacemaker after a TAVI procedure. A study published in late 2014 using this tool in monitoring post TAVI conduction disorders on a small number of patients, other studies used the same tool in other cardiac pathologies.

We propose to carry out an observational study of patients implanted with a pacemaker using AAI SafeR® mode after a TAVI procedure. This study aims to define the persistence or not of high-grade AVB beyond seven days after the procedure, based on the analysis of PM memories, and define definitive cardiac pacing indications after TAVI procedure.

II.OBJECTIFS of the study

Primary End point :

Prove persistence or not of high grade conduction disturbances beyond seven days after a TAVI procedure in patients in sinus rhythm implanted with a Sorin dual chamber Pacemaker programmed in AAI SafeR mode.

Secondary End point:

Define the factors associated with a higher risk of high level A-V block after a TAVI procedure. This analysis will allow us to better define the final pacing indications after TAVI.

III.CRITERIA of JUDGEMENT

High level persistent A-V Block in patients after TAVI procedure is defined:

- Either by the analysis of the pacemaker memories showing the switches to DDD mode after one or more of these three reasons:
 - a succession of at least 2 consecutive blocked P waves
 - more than 3 blocked P waves among 12 consecutive cycles
 - ventricular pause for over 2 seconds with at least one blocked P wave
- Either by the presence of a high level AVB during the pacemaker interrogation

We classify as transitional AVB (D7 persistent, non-persistent beyond 1 month), and permanent AVB (persistent beyond 1 month).

IV. POPULATION STUDIED

Inclusion criterias:

All patients over 18 years who underwent implantation of a TAVI and that were implanted during the hospitalization with a dual chamber pacemaker Sorin®, set in AAI SafeR ® or AAI SafeR-R® mode.

Exclusion criterias:

- Patients with life expectancy at hospital discharge estimated as less than 1 year
- TAVI procedure failure
- Patients refusing to be involved in the study
- Patients implanted with a PM of a brand different than Sorin® during the hospital phase or implanted Sorin® PM but not set in a AAI or AAI SafeR SafeR-R mode
- Patients with PM implant before TAVI
- Permanent AF at the implantation time
- Patients with Single or Triple chamber PM

V.INVESTIGATION METHODE

We propose a prospective, observational, multicenter study of patients implanted with a Sorin® PM set in a AAI SafeR® or AAI SafeR-R® mode, after a TAVI procedure. The follow-up period will be at least 1 year after implantation of the pacemaker. Only data related to monitoring of A-V conduction disorders is collected during this study.

The PM implantation decision and the choice of treatments are up to the local investigators.

The scientific committee has to validate the protocol, ensure the scientific and ethical oversight of the study, ensure the confidentiality of the study and the compliance the investigators with the commitments of this protocol and good clinical practices rules and ethics.

An annual report will be provided to the scientific committee and the participating centers.

Submissions for communications or publications will be sent to the scientific committee and sponsors before presentation or publication.

VI. REGULATORY AND PHARMACOVIGILANCE

The study will not alter the therapeutic attitude of medical teams. The protocol has no influence on medical prescription in the hospital and in the long-term monitoring. No visit outside the conventional monitoring visits or special exams are required as part of the study. The study will therefore not need the authorization of people protection committee (apart from an advisory opinion on the non-interventional nature of the study) or AFSSAPS. It was submitted to the CCTIRS (advisory committee on the treatment of research information in health matters) and the CNIL (national commission on informatics and liberties), and has received the necessary authorizations.

The principal investigator agrees to remind health professionals involved in the study their legal and regulatory obligations (Articles L. 5121-25 and R. 5121-161 of the public health code). The principal investigator is not responsible for the declaration of adverse events related to the subject of the study and occurred during it.

VII. Collection, processing and data transfer

According to the texts about law and liberties last modified the 6 January 1978, all patients before involved in the study will receive an information note on the transmission and use of their data (Annex 1). Patients may orally refuse to participate to the study.

Data entry will be undertaken by the clinical research associate and the investigator in each participating center, bound by professional secrecy : inclusion data at the first postoperative visit, and during monitoring visits at the end of the study. The entry will be made on an electronic case report form (e-CRF), protected by passwords. The analysis will be performed on a computer database specifically created for this study. The access to the database will be secured and customized by a user name and password. The PM interrogation files will be sent to the investigating center, for a centralized reading of the memorized EGM by an independent adjudication committee.

The electronic case report forms will be stored respecting the anonymity of patients. Patients will be identified by an inclusion number, the first three letter of their first name, the first two letters of their last name, and their month and year of birth. Each

center will have to store the correspondence between the inclusion numbers and identity of the patient on a list that must remain confidential under the responsibility of the investigator of the center.

The database of informations collected will not be duplicated and will be stored on a single computer, protected by access codes, under the responsibility of the principal investigator in the center.

Patient information notes, protocol, e-mails, trial documents and patient identity match list with the inclusion numbers will be stored by the centers for at least 15 years. The anonymised data will be kept by the principal investigator of the study for the same duration after the end of the research, in accordance with good clinical practice guide.

VIII. NATURE OF COLLECTED DATA

The data collected allow us to characterize our population and to determine the variables associated with the primary and secondary endpoints, only as part of the objective of our research.

The collected variables are listed in the report form (Appendix 2)

IX. DATA ANALYSIS METHOD

The registry analysis will be conducted by the Statistical Service of the Annecy regional public hospital (Centre Hospitalier Annecy Genevois). We will describe the characteristics of our population (age, sex, cardiac history, cardiac functional signs, EKG, data from the TAVI procedure (type and size of implant, valvular calcification, implant height, surgical approach). According to the main goal, we will determine the incidence of high level A-V block in patients involved in the study, after reviewing and validation of the PM memories by an independent adjudication committee. In accordance with the secondary objective, we will study the factors associated with the primary outcome: gender, age, preexisting conduction disturbances (complete right bundle branch block, left anterior hemiblock, first degree A-V block), high grade AVB during the TAVI procedure, worsening of conduction disturbances during the procedure or within the next hour (appearance of a left bundle branch block, QRS widening beyond 120ms, prolongation of PR beyond 200ms), worsening of HV conduction time immediately after the procedure TAVI or later (if scanning is performed), implantation of a Medtronic® CoreValve prosthesis (compared to a Edwards® Sapien prosthesis), height of the implantation of the valve, oversizing.

X. STUDY DURATION AND NUMBER OF PATIENTS INCLUDED

With the assumption of a frequency of 50% endpoint and a power of 80%, with 200 patients included the 95% confidence interval would be 43-57% (Wilson's method) (5).

Considering that 20% of patients enrolled will be lost we plan to include 250 patients. This study will begin in June 2014 for a period of 2 years.

XI. REFERENCES

1. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med*. 2012 May 3;366(18):1705-15.
2. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013 Aug;34(29):2281-329.
3. Erkapic D, De Rosa S, Kelava A, Lehmann R, Fichtlscherer S, Hohnloser SH. Risk for permanent pacemaker after transcatheter aortic valve implantation: a comprehensive analysis of the literature. *J Cardiovasc Electrophysiol*. 2012 Apr;23(4):391-7.
4. Siontis GC, Juni P, Pilgrim T, Stortecky S, Bullesfeld L, Meier B, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol*. 2014 Jul 15;64(2):129-40.
5. Bjerre Thygesen J, Loh PH, Cholteesupachai J, Franzen O, Sondergaard L. Reevaluation of the indications for permanent pacemaker implantation after transcatheter aortic valve implantation. *J Invasive Cardiol*. 2014 Feb;26(2):94-9.
6. Bates MG, Matthews IG, Fazal IA, Turley AJ. Postoperative permanent pacemaker implantation in patients undergoing trans-catheter aortic valve implantation: what is the incidence and are there any predicting factors? *Interact Cardiovasc Thorac Surg*. 2011 Feb;12(2):243-53.
7. Frohlig G, Gras D, Victor J, Mabo P, Galley D, Savoure A, et al. Use of a new cardiac pacing mode designed to eliminate unnecessary ventricular pacing. *Europace*. 2006 Feb;8(2):96-101.
8. Bleiziffer S, Ruge H, Horer J, Hutter A, Geisbusch S, Brockmann G, et al. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2010 May;3(5):524-30.
9. Erkapic D, Kim WK, Weber M, Mollmann H, Berkowitsch A, Zaltsberg S, et al. Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. *Europace*. 2010 Aug;12(8):1188-90.
10. Courvoisier DS, Combescure C, Agoritsas T, Gayet-Ageron A, Perneger TV. Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure. *J Clin Epidemiol*. 2011 Sep;64(9):993-1000.