BMJ Open Prospective observational study on the accuracy of predictors of high-grade atrioventricular conduction block after transcatheter aortic valve implantation (CONDUCT-TAVI): study protocol, background and significance

Karan Rao1,2,3 Kunwardeep Bhatia,1 Bernard Chan,1,2 Mitchell Cowan,1,3 Natasha Saad,1,3 Alexandra Baer,3 Hari Sritharan,1 Ingrid Bromhead,1 David Whalley,1,3 Usaid K Allahwala,1,2 Peter Hansen,3,3 Ravinay Bhindi1,2,3


ABSTRACT

Introduction Aortic stenosis is the most common cardiac valve pathology worldwide and has a mortality rate of over 50% at 5 years if left untreated. Transcatheter aortic valve implantation (TAVI) is a minimally invasive and highly effective alternative treatment option to open-heart surgery. High-grade atrioventricular conduction block after transcatheter aortic valve implantation (TAVI) is one of the most common complications after TAVI and requires a permanent pacemaker. Due to this, patients are typically monitored for 48 hours post TAVI, however up to 40% of HGAVB may delayed, and occur after discharge. Delayed HGAVB can cause syncope or sudden unexplained cardiac death in a vulnerable population, and no accurate methods currently exist to identify patients at risk.

Methods and analysis The prospective observational study on the accuracy of predictors of high-grade atrioventricular conduction block after transcatheter aortic valve implantation (CONDUCT-TAVI) trial is an Australian-led, multicentre, prospective observational study, aiming to improve the prediction of HGAVB, after TAVI. The primary objective of the trial is to assess whether published and novel invasive electrophysiology predictors performed immediately before and after TAVI can help predict HGAVB after TAVI. The secondary objective aims to further evaluate the accuracy of previously published predictors of HGAVB after TAVI, including CT measurements, 12-lead ECG, valve characteristics, percentage oversizing and implantation depth. Follow-up will be for 2 years, and detailed continuous heart rhythm monitoring will be obtained by inserting an implantable loop recorder in all participants.

Ethics and dissemination Ethics approval has been obtained for the two participating centres. Results of the study will be submitted for publication in a peer-reviewed journal.

Trial registration number ACTRN12621001700820.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study has broad inclusion criteria which increases the generalisability of the results.
⇒ This study uses highly accurate continuous cardiac monitoring with implantable loop recorders for a follow-up period of 2 years to screen for high-grade atrioventricular block after transcatheter aortic valve implantation (TAVI).
⇒ All conduction events are assumed to be secondary to the TAVI, and the influence of confounders such as age and pre-existing undiagnosed conduction disease will be difficult to estimate.

INTRODUCTION

Aortic stenosis (AS) is the most common cardiac valve pathology, and often manifests with the classical triad of dyspnoea, angina and syncope.1 Severe AS has a mortality of over 50% at 5 years if untreated and affects 1.5% of the Australian population over the age of 55 and 3.5% over 75 years.1 Transcatheter aortic valve implantation (TAVI) is a minimally invasive treatment option for patients with severe symptomatic AS with comparable outcomes to surgical valve replacement across all patient risk groups.2 3 The American Society of Thoracic Surgeons/ American College of Cardiology Transcatheter Valve Therapy registry data confirms frequency of TAVI has now surpassed surgical aortic valve replacements since 2019,4 and Australia is also following a similar trend. In 2021, the cost of TAVI in Australia was estimated at $A53 164, based on an average hospital stay of 6 days.5 With TAVI approved for low-risk patients,6 and a shift to intervene
at earlier disease phases, coupled with an ageing global population, there is an urgent need for studies to streamline TAVI, improve its cost-effectiveness and optimise patient outcomes.

Due to the proximity of the aortic valve annulus with the atrioventricular (AV) node and bundle of His, high-grade atrioventricular block (HGAVB) is extremely common after TAVI, occurring in 9–26% of cases.7–9 HGAVB is defined as clinically significant forms of heart block, specifically to second degree Mobitz Type II and third degree (complete) heart block. The pathophysiology is believed to be via direct mechanical compression of the ventricularised valve frame on the left ventricular outflow tract, and specifically the superficial membranous septum, which contains the normal conduction pathway. The currently known predictors include age, baseline right bundle-branch block, membranous septum length, implantation depth, aortic valve calcification distribution, prosthesis oversizing and use of a self-expanding prosthesis; however, these predictors are limited by poor sensitivity or specificity.8–10,12 Newer valve designs aim to provide a more streamlined profile with reduced radial tension to help reduce pacemaker requirements, and higher implantations have also reduced the risk of directly compressing the membranous septum.13 Currently, patients are typically monitored in hospital for 48 hours after TAVI to assess for the development of HGAVB, and treatment is with a pre-discharge permanent pacemaker in that instance. Furthermore, as the prosthesis continues to expand and settle into the aortic annulus, up to 40% of HGAVB may be delayed, occurring after 48 hours, up until 2 years.14 This may result in falls, syncope or even sudden cardiac death following discharge in a potentially vulnerable elderly population.

Tachyarrhythmias are less common following TAVI however, new-onset atrial fibrillation (NOAF) has been reported in up to 11% of patients at 1-month and 25% of patients at 2-year follow-up.15 Additionally, it has recently been published that NOAF, occurring up until 1-year post TAVI, is independently associated with increased risk of death, stroke and rehospitalisation.16 Currently, the only known predictors of NOAF are patient factors of age and left atrial volume, however other possible procedural precipitants are not well known.

Study rationale

Currently, there is no accurate algorithm to identify patients likely to develop HGAVB after TAVI. Similarly, procedural predictors of atrial fibrillation (AF) following TAVI are not well understood. Right atrial (RA) pacing has been shown to be a sensitive, but not a specific test to predict HGAVB after TAVI.17 Krishnaswamy et al8,7 demonstrated that patients who do not exhibit RA pacing induced AV block at a cycle length (CL) ≥500 ms (AV Wenckebach CL) immediately after TAVI have a very low risk of requiring permanent pacemaker implantation. However, the positive predictive value of this was low (13%), and thus this method does not serve clinical utility in predicting HGAVB. We hypothesise that the positive predictive value of RA pacing to predict HGAVB could be improved by performing it both prior to and immediately after TAVI. We hypothesise that patients who develop a significant change to the CL at which they develop AV Wenckebach are at the highest risk of developing HGAVB after TAVI.

Furthermore, AV block caused by TAVI is mostly due to His bundle injury via mechanical compression of the membranous septum. His bundle function is only indirectly assessed by RA pacing and can be directly assessed by measuring the change in HV (His to ventricle) interval with TAVI. Prolongation of the HV interval has previously been shown to be a predictor of HGAVB after TAVI.18,19 However, its added utility over RA pacing is unknown, and we aim to test our hypothesis that combining the two results may be a more accurate predictor of HGAVB.

Study objectives

The primary objective of the study is to determine the sensitivity and specificity of novel electrophysiology study derived predictors of HGAVB after TAVI. The secondary objective is to evaluate a combination of other previously published and novel predictors of HGAVB after TAVI, as well as determine the proportion of patients who develop HGAVB and NOAF over a 2-year follow-up period following TAVI. This is discussed in greater detail below under ‘Study Outcomes’.

METHODS AND ANALYSIS

CONDUCT-TAVI is a multicentre, open label, prospective observational study, designed to assess the accuracy of published and novel predictors of HGAVB after TAVI. Consecutive patients, who are eligible and provide informed consent will be included, and all patients will undergo pre-procedure CT, 12-lead ECG as well as pre-TAVI and post-TAVI targeted electrophysiology study. All patients will receive an implantable loop recorder following TAVI. Follow-up will be for 2 years after TAVI. The study protocol is also published and available on the Australia and New Zealand clinical trials registry. The study has been approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD HREC).

The study began recruiting in October 2021 and recruitment anticipated to be completed by December 2023. The study will end 2 years after the last recruited patient undergoes TAVI, that is, once all follow-up period is completed.

Study population

All consecutive patients that are referred for elective TAVI to Royal North Shore Public Hospital and North Shore Private Hospital will be screened for inclusion. Inclusion criteria include an age of at least 18 years and the ability to provide informed consent. Patients with permanent pacemakers or prior aortic valve replacements will be
excluded (figure 1). Patients may withdraw at any time, and replacement participants will not be recruited.

Recruitment
The study team at each enrolling centre will identify suitable patients through the Structural Heart Team meeting. The Structural Heart Team meeting is a formal requirement prior to TAVI, whereby each patient referred for TAVI will be discussed in a multidisciplinary setting prior to acceptance. Patients will be screened and approached for consent during pre-admission clinical review prior to their TAVI. Consent will be obtained with a third-party (witness) present. Enrolled patients will receive a study enrolment identification number, and this will be documented in the participants medical record and study documents.

CT analysis
Prior to TAVI, all patients undergo pre-procedure ECG-gated multidetector CT. Image acquisition and sequences will be as per protocol prior to TAVI and will not be mandated by the trial protocol. However, all images will be reviewed independently by study investigators using 3mensio imaging software (Pie Medical Imaging, Netherlands). The following measurements will be collected for analysis:

- Membranous septal length (mm).
- Annular diameter, maximum and minimum (mm).
- Annular perimeter and area (mm, mm$^3$).
- Coronary cusp (left, right and non-coronary) upper, basal and left ventricular outflow tract (LVOT) level calcification.
- Left and right coronary artery heights (mm).

The membranous septum length is a CT-based measurement of the non-muscular and thinnest part of the interventricular septum and is found in the commissure between the non and right aortic cusp. It is clinically relevant as the bundle of His traverses through the inferior segment of the membranous septum. As such, in patients with a longer membranous septum, the bundle of His will cross deeper in the left ventricular outflow tract, thus seemingly being more protective of complete heart block due to TAVI. Subsequently, implanting higher than the membranous septum length has now been validated to reduce pacemaker rates.20 The membranous septum will be measured using a previously published technique,21 by placing cross-hairs at the commissure between the non and right aortic cusp and measuring the length of the infra-annular portion from the virtual basal ring to the muscular septum inferiorly.

TAVI procedure details
All patients will undergo TAVI at Royal North Shore Hospital or North Shore Private Hospital. Both centres perform the same procedure with the same operators (RB and PH). All cases will have an anaesthetist, and cases are primarily planned with sedation and local anaesthesia, however the escalation to general anaesthesia may be a clinical decision made at the time of the procedure by the anaesthetist and operators and is not dictated by the trial protocol. The study protocol does not discriminate for TAVI access site, however both centres primarily perform transfemoral TAVI, with primary ultrasound-guided...
right femoral artery access and either secondary femoral artery or radial artery access. Ultrasound-guided trans-femoral venous access will be obtained for passage of the multielectrode electrophysiology catheter (BIOTRONIK, Berlin, Germany).

Both centres use two transcatheter heart valves, the balloon-expandable Sapien 3 system (Edwards Life-sciences, Irvine, USA), and the self-expandable Evolut (Medtronic, Dublin, Ireland) system. Valve choice is primarily based on clinical reasoning and is not mandated by the study protocol. Over the course of 2021, the valve types used in the two involved centres were balanced (55% self-expanding and 45% balloon-expanding), which is expected to be similar over the course of the study. The implantation strategy will aim for the safest and highest deployment, by using the cuff overlap technique for the self-expandable platform and the high deployment technique for the balloon-expandable platform following implantation, the implantation depth (mm) will be measured on coplanar fluoroscopy.

Following TAVI, patients will undergo loop recorder implantation. They will be monitored in the relevant hospital’s coronary care unit for a period of 48 hours with ward-based cardiac telemetry and will be discharged usually on days 3–5 based on clinical discretion. Discharge timing is not mandated by the study protocol.

ECG analysis
All patients will undergo 12-lead ECG using standard methodology at the following time points: Immediately before and after TAVI, 4 hours post TAVI, 24 hours post TAVI, 28 days post TAVI, 6 months, and 12 months post TAVI. All patients will undergo rapid RA pacing and HV interval measurements immediately before and after TAVI.

Rapid RA pacing
RA pacing will be performed immediately before valve deployment, and then immediately after deployment, using a multielectrode catheter in the right atrium and measured via a mobile electrophysiology system. This catheter will replace the commonly used temporary pacing wire in the right ventricle. Two methods of atrial pacing will be performed. The first is as described by Krishnaswamy et al., where RA pacing was incremented by 10 beats per minute (bpm) from 70 bpm to 120 bpm for 20 beats at each increment until AV Wenckebach was observed. AV Wenckebach is defined as progressive PR interval prolongation followed by a non-conducted paced atrial beat and a shorter return PR interval. If the patient’s atrial rate is above 70 bpm then the manoeuvre should be started at the next increment above the patient’s baseline heart rate. A second method of RA pacing involves incremental pacing starting at either 1000 ms (or 60 ms above the patients resting CL). The pacing CL should be progressively shortened by 10 ms decrements every three beats until AV Wenckebach occurs or until a maximum CL of 400 ms is reached.

RA pacing will not be performed in patients who are in an atrial tachyarrhythmia or ventricular pacing dependent at the time the atrial pacing procedure is to be performed. Patients who have transient AV block during TAVI deployment which recovers during the procedure should still go on to have RA pacing performed.

Measurement of HV interval
The HV interval will be measured using the same multielectrode catheter that was used previously for RA pacing, using the same standardised mobile electrophysiology system. The His signal will be obtained by positioning the catheter in the lower RA and defined as the intervening signal between the atrial and ventricular signal. This interval must be reproducible (±2 ms) over at least three beats. The multielectrode catheter will be removed at the end of the procedure. If there is a clinical indication for continued pacing (e.g. transient or complete heart block), this multielectrode catheter will remain in place as a temporary pacing wire until permanent pacemaker implantation.

Loop recorder implantation
A loop recorder may be implanted immediately after the TAVI procedure or prior to discharge from hospital. All loop recorders will be supplied by BIOTRONIK (Berlin, Germany) in good faith to Royal North Shore Hospital. Loop recorders will not be routinely removed unless there is a specific indication to do so, or if patients wish to withdraw from the study. All loop recorders will be distributed with CardioMessenger Home Monitoring (BIOTRONIK, Berlin, Germany), which will be reviewed daily by the study team. All loop recorders will be programmed to detect bradycardia below 40 bpm, tachycardia above 180 bpm, pauses over 3 s, as well as irregular heart rates (R-R variability) and patient-triggered recordings.

Follow-up
Research personnel from the study team will follow patients throughout their time in hospital and will contact patients by phone for an in-person follow-up appointment at 28 days (1 month), 6 months, 12 months and 24 months after TAVI (see figure 2). If the participant is unable to be contacted, the treating physician or local doctor will be contacted. Patients with implantable loop recorders will be followed primarily using remote home monitoring (CardioMessenger, BIOTRONIK), which enables automatic daily transmission of data with an alert system, which will be reviewed by research personnel.

If HGAVB, or NOAF, is detected by the research personnel team, the treating physician will be informed immediately and further management decisions will be left to the treating physician and is not dictated by the study protocol. Any new pacemaker implantations will be carefully recorded.

Currently, immediate post procedure pacemaker implantation is left to the discretion of the heart team and TAVI operators. Clinical judgement is used on
a case-by-case basis. Typically, patients with high-risk features such as perioperative complete heart block or Mobitz II second degree heart block are managed with a permanent pacemaker. The exact indication for insertion time and from the procedure will be recorded and evaluated. Please see table 1 below for a summary of the schedule.

Primary outcomes and assessment
The primary outcome will be to evaluate the sensitivity, specificity, positive predictive value and negative predictive value of the following novel and previously published electrophysiology predictors of HGAVB after TAVI. First, RA pacing and AV Wenckebach results: 50 ms increase in AV Wenckebach CL after TAVI, 50 ms increase in AV Wenckebach CL AND 13 ms increase in HV interval after TAVI and absolute AV Wenckebach CL ≥ 500 ms immediately before and/or after TAVI. Second, related to the HV interval results: 13 ms increase in HV interval after TAVI, and absolute HV interval post TAVI > 65 ms. ECG findings immediately prior and post TAVI, 4 hours post TAVI and 24 hours post TAVI. These include right bundle branch block, left bundle branch block, left anterior hemiblock, left posterior hemiblock, first degree AV block, AV Wenckebach, AF, atrial flutter. And finally, the role of transient HGAVB during TAVI, in predicting HGAVB after TAVI.

Secondary outcomes and assessment
The secondary outcomes will be to evaluate the area under the receiver operating characteristic curve (AUC) for the following novel and previously published predictors of HGAVB after TAVI:

- Change in AV Wenckebach CL after TAVI (ms).
- Percentage change in AV Wenckebach CL after TAVI (%).
- Change in HV interval after TAVI (ms).
- AV Wenckebach CL after TAVI (ms).
- AV Wenckebach CL prior to TAVI (ms).
- HV interval after TAVI (ms).
- HV interval before TAVI (ms).
- Non-coronary cusp device-landing zone calcium volume (mm$^3$).
- Membranous septum length (mm).
- Difference between membranous septum length and implantation depth (mm).
- Implantation depth (mm)—this will be consistently obtained using a double cusp overlap (right anterior oblique-caudal) projection acquisition, with measurement of the ventricular aspect of the valve frame to the non-coronary cusp on aortography.

Furthermore, we aim to determine the proportion of patients that develop delayed HGAVB at the following intervals after TAVI:

- 48 hours, 72 hours, 7 days, 28 days, 6 months, 12 months and 24 months.
We also aim to determine the proportion of patients that develop new AF or flutter after TAVI. To determine the atrial and ventricular pacing percentages in patients that receive a single or dual chamber pacemaker at the following intervals after TAVI:

- 28 days, 6 months, 12 months and 24 months.
- Prespecified subgroup analysis will be conducted by:
  - Valve type (balloon expanding or self-expanding transcatheter heart valve).
  - Presence of AF or flutter immediately prior to TAVI.
  - Presence of AF or flutter immediately after TAVI.

Additional outcome measures of accuracy, positive likelihood ratio and negative likelihood ratio will be calculated for both the primary outcomes. Optimal cut-points will be calculated for the AUC for the secondary outcomes.

**Sample size**

We estimated the prevalence of HGAVB after TAVI up until 2 years to be 15%. A sample size of 194 produces a two-sided 95% CI with a width equal to 0.15 when the sample sensitivity is 0.98, and the prevalence is 0.15 (Wilson score interval). Assuming a dropout rate of 5%, a total enrolment sample size of 205 patients is required.

**Analysis**

For each prespecified predictor in the primary outcome, the following outcomes will be calculated. Positive predictive value, negative predictive value, sensitivity, specificity, accuracy, positive likelihood ratio and negative likelihood ratio. Area under the receiver operator characteristic will also be calculated for predefined variables.

**Study management and structure**

Royal North Shore Public Hospital, Sydney, Australia, will be the core centre for study management. The website and data interface setup, ongoing data analysis and safety monitoring will be performed at Royal North Shore Hospital. North Shore Private Hospital is the second enrolling site, and is located on the same campus in Sydney, Australia.

**Interim analyses**

The primary endpoint will be assessed at 1 month after the last patient undergoes TAVI. The primary and secondary endpoint will be assessed at 12 months and 24 months after the last patient undergoes TAVI.

**Data statement**

Research personnel from the study team will closely monitor study data based at Royal North Shore Hospital. Each site will nominate one or more research personnel to collect data and fill in the case report form after de-identification on the secure cloud-based research software REDCap (Research Electronic Data Capture) (Vanderbilt University, Tennessee, USA). REDCap, hosted by NSLHD is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

**Data**

Data for the study will be collected from multiple sources including patient interviews as well as reviewing paper and electronic medical records. The data from loop recorders will be transmitted through a home monitoring device CardioMessenger (BIOTRONIK, Berlin, Germany) to the BIOTRONIK Home Monitoring Service Center via mobile communication every 24 hours.

Data will be stored on the secure Northern Sydney Local Health District REDCap server. Study investigators will have individual usernames and passwords to access the study database. Only select investigators can participate in data entry and a separate delegate will oversee storage. Data from loop recorders will be stored on secure BIOTRONIK servers, which are certified by the International Organization for Standardization’s (ISO) ISO/IEC 27001:2013. ISO’s certification of BIOTRONIK Home Monitoring provided independent verification that BIOTRONIK professionally protects the service’s availability, privacy and integrity.

The project has been approved by the NSLHD HREC (2021/ETH01039), and any deviations or amendments to the protocol will be submitted to the committee prior to implementation.

**Timeline**

Recruitment began in October 2021 and is anticipated to be completed by December 2023. The study will end 2 years after the last recruited patient undergoes TAVI. Together, both centres perform on average 150–170 TAVI procedures per year, and as such, the proposed 2 years is a feasible and achievable timeline to complete recruitment.

**Procedural time and safety concerns**

The total time taken for the procedure (skin-to-needle until loop recorder implantation) will be recorded for each study. We anticipate that the procedural time will increase by roughly 12–15 min, due to the targeted electrophysiology (EP) study and loop recorder implantation. Despite the added procedural time, we hypothesise that performing a targeted EP study pre and post TAVI will help to risk stratify patients for early and delayed HGAVB. Better prediction of HGAVB will help us move towards same-day discharge, which would alleviate the chronic issue of bed availability in busy public hospital systems. This will improve accessibility of TAVI to patients worldwide and improve its cost-effectiveness.

**Patient and public involvement**

There was no patient or public involvement in the design, conduct, reporting or dissemination plans of this research study. Any clinically relevant information detected during the study will be relayed to their treating cardiologist, as the research protocol does not dictate treatment.
Significance

HGA VB remains one of the most common complications of TAVI, and requires the implantation of a permanent pacemaker, causing a significant burden on the patient and hospital system. Delayed HGA VB may be particularly dangerous, as it commonly occurs after discharge, in a vulnerable and often frail elderly population, with risk of falls, syncope and even sudden cardiac death. While there are various known risk factors for HGA VB, their clinical utility is limited by poor sensitivity or specificity, and currently no accurate risk stratification algorithm exists. This prospective multicentre observational study employs a targeted electrophysiology study immediately before and after TAVI, coupled with other published predictors, to predict patients at risk of developing HGA VB, which is monitored via an implantable loop recorder for a period of 2-years. The results of this study will improve our prediction algorithm for HGA VB and pacemakers, and as such, help to streamline and optimise TAVI, reduce hospital lengths of stay and most importantly, improve patient outcomes.

ETHICS AND DISSEMINATION

This study has been approved by the Northern Sydney Local Health District (NSLHD) Human Research Ethics Committee (HREC). Any adverse events related to the research study are reported directly to this ethics committee.

The authors aim to publish the research data in peer-reviewed journals, as well as present results in national and international meetings.

Contributors KR, KB, BC, MC, NS, AB, HS, IB, DW, UKA, PH and RB were all involved in the formulation of the trial protocol and finalisation. KR, KB and BC were involved in the ethics application, and data collection. KR, AB, PH and RB were involved with writing and editing this manuscript.

Funding The trial is funded by the Royal North Shore Cardiology Department (Sydney, Australia). Implantable loop recorders are being provided in good faith by BIOTRONIK (Berlin, Germany), grant number FF074. The mobile electrophysiology system (EP Perfect) is being loaned by BIOTRONIK (Berlin, Germany). This is an investigator initiated and led clinical trial, with the industry-sponsor having no input into the scientific protocol, data analysis or writing of scientific manuscripts.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD Karan Rao http://orcid.org/0000-0003-4689-9982

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