CJC Open 5 (2023) 611–618

Study Design

Rationale and Design of the Randomized Bayesian Multicenter COME-TAVI Trial in Patients With a New Onset Left Bundle Branch Block

Lena Rivard, MD, MSc,[a] Isabelle Nault, MD,[b] Andrew D. Krahn, MD,[c] Benoit Daneault, MD,[d] Jean-Francois Roux, MD,[d] Madhu Natarajan, MD,[e] Jeffrey S. Healey, MD, MSc,[e] Kenneth Quadros, MD,[f] Roopinder K. Sandhu, MD, MPH,[f] Remi Kouz, MD,[g] Isabelle Greiss, MD,[h] Peter Leong-Sit, MD,[i] Jean Baptiste Gourraud, MD,[j] Walid Ben Ali, MD, PhD,[k] Anita Asgar, MD, Msc,[a] Martin Aguilar, MD, PhD,[a] Raoul Bonan, MD,[a] Julia Cadrin-Tourigny, MD, PhD,[a] Raymond Cartier, MD,[k] Jean-Francois Dorval, MD,[a] Marc Dubuc, MD,[a] Nicolas Dürrleman, MD, MSc,[k] Katia Dyrda, MD,[a] Peter Guerra, MD,[a] Marina Ibrahim, MD, MSc,[k] Reda Ibrahim, MD,[a] Laurent Macle, MD,[a] Blandine Mondesert, MD,[a] Emmanuel Moss, MD, MSc,[k] Alexandre Raymond-Paquin, MD,[a] Denis Roy, MD,[a] Rafik Tadros, MD, PhD,[a] Bernard Thibault, MD,[a] Mario Talajic, MD,[a] Anna Nozza, MSc,[l] Marie-Claude Guertin, PhD,[l] and Paul Khairy, MD, PhD[a]

[a] Department of Cardiology, Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; [b] Department of Cardiology, Quebec Heart and Lung Institute, Quebec City, Quebec, Canada; [c] Centre for Cardiovascular Innovation, University of British Columbia, Vancouver, British Columbia, Canada; [d] Department of Cardiology, Université de Sherbrooke, Sherbrooke, Quebec, Canada; [e] Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [f] Division of Cardiology, Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada; [g] Department of Cardiology, Hopital Sacre-Coeur de Montreal, Montreal, Quebec, Canada; [h] Department of Cardiology, Centre Hospitalier de Université de Montréal, Montreal, Quebec, Canada; [i] Department of Cardiology, Western University, London, Ontario, Canada; [j] Department of Cardiology, Centre Hospitalier Nantes, Nantes, France; [k] Department of Cardiac Surgery, Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; [l] Montreal Health Innovations Coordinating Center, Montreal Heart Institute, Montreal, Quebec, Canada

ABSTRACT

Patients with new-onset left bundle branch block (LBBB) after transcatheter aortic valve implantation (TAVI) are at risk of developing delayed high-degree atrioventricular block. Management of new-onset

RÉSUMÉ

Les patients chez qui un bloc de branche gauche (BBG) est récemment apparu à la suite de l'implantation valvulaire aortique par cathéter (IVAC) présentent un risque de bloc auriculoventriculaire de haut degré

Since the first-in-human procedure in 2002, transcatheter aortic valve implantation (TAVI) has become a well-established therapeutic option for severe aortic stenosis, and TAVI volume has recently surpassed that of surgical aortic valve replacement in the US.[1] New-onset conduction abnormalities, including left bundle branch block (LBBB) and atrioventricular (AV) block are the most frequent complications after transcatheter aortic valve implantation.[2-4] The incidence of new-onset LBBB varies—from 3% to 30% with the balloon-expandable Edwards SAPIEN and SAPIEN XT (ESV) systems (Edwards Lifesciences, Irvine, CA), up to 35% to 65% with the self-expanding Medtronic Core Valve (MCV) system (Medtronic, Minneapolis, MN).[5-9] Patients who develop LBBB after TAVI are at risk for AV block,

Received for publication March 25, 2023. Accepted May 22, 2023.

Corresponding author: Dr Lena Rivard, Department of Electrophysiology, Montreal Heart Institute, 5000 Belanger St., Montreal, Quebec H1T 1C8, Canada. Tel.: +1-514-376-3330; fax: +1-514-593-2496.
E-mail: lena.rivard@icm-mhi.org

See page 617 for disclosure information.

https://doi.org/10.1016/j.cjco.2023.05.009
2589-790X/© 2023 The Authors. Published by Elsevier Inc. on behalf of the Canadian Cardiovascular Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

LBBB post-TAVI remains controversial. In the Comparison of a Clinical Monitoring Strategy Versus Electrophysiology-Guided Algorithmic Approach in Patients With a New LBBB After TAVI (COME-TAVI) trial, consenting patients with new-onset LBBB that persists on day 2 after TAVI, meeting exclusion/inclusion criteria, are randomized to an electrophysiological study (EPS)-guided approach or 30-day electrocardiographic monitoring. In the EPS-guided approach, patients with a His to ventricle (HV) interval $\geq$ 65 ms undergo permanent pacemaker implantation. Patients randomized to noninvasive monitoring receive a wearable continuous electrocardiographic recording and transmitting device for 30 days. Follow-up will be performed at 3, 6, and 12 months. The primary endpoint is a composite outcome designed to capture net clinical benefit. The endpoint incorporates major consequences of both strategies in patients with new-onset LBBB after TAVI, as follows: (i) sudden cardiac death; (ii) syncope; (iii) atrioventricular conduction disorder requiring a pacemaker (for a class I or IIa indication); and (iv) complications related to the pacemaker or EPS. The trial incorporates a Bayesian design with a noninformative prior, outcome-adaptive randomization (initially 1:1), and 2 prespecified interim analyses once 25% and 50% of the anticipated number of primary endpoints are reached. The trial is event-driven, with an anticipated upper limit of 452 patients required to reach 77 primary outcome events over 12 months of follow-up. In summary, the aim of this Bayesian multicentre randomized trial is to compare 2 management strategies in patients with new-onset LBBB post-TAVI—an EPS-guided approach vs noninvasive 30-day monitoring. Trial registration number: NCT03303612.

tardif. La prise en charge d'un BBG récemment apparu après une IVAC demeure controversée. Dans le cadre de l'essai COME-TAVI (*Comparison of a Clinical Monitoring Strategy Versus Electrophysiology-Guided Algorithmic Approach in Patients With a New LBBB After TAVI*, ou comparaison d'une stratégie de surveillance clinique, par rapport à une approche guidée par étude électrophysiologique et fondée sur un algorithme, chez des patients présentant un BBG d'apparition récente à la suite d'une IVAC), des patients qui présentent un BBG d'apparition récente persistant le 2e jour après une IVAC, qui répondent aux critères d'admissibilité et qui ont donné leur consentement sont répartis aléatoirement pour être suivis à l'aide d'une approche guidée par une étude électrophysiologique (EEP) ou faire l'objet d'une surveillance électrocardiographique d'une durée de 30 jours. Un stimulateur cardiaque est implanté chez les patients du groupe de l'EEP dont l'intervalle HV (temps de conduction dans le tronc du faisceau de His jusqu'aux ventricules) est $\geq$ 65 ms. Les patients du groupe de surveillance non invasive reçoivent un dispositif portable d'enregistrement et de transmission continue de données électrocardiographiques pour une période de 30 jours. Le suivi sera réalisé aux 3e, 6e et 12e mois. Le critère d'évaluation principal est un paramètre composite conçu afin de saisir le bienfait clinique net. Il comprend les conséquences majeures des deux stratégies chez les patients présentant un BBG d'apparition récente après une IVAC, comme suit : (i) mort subite d'origine cardiaque; (ii) syncope; (iii) trouble de la conduction auriculoventriculaire nécessitant la pose d'un stimulateur cardiaque (pour une indication de classe I ou IIa); et (iv) complications relatives au stimulateur cardiaque ou à l'EEP. L'essai intègre une conception bayésienne avec une répartition aléatoire (dans un rapport initial de 1:1) antérieure non informative adaptée aux résultats et deux analyses intermédiaires définies au préalable lorsque 25 % et 50 % du nombre anticipé des critères d'évaluation principaux seront atteints. L'essai est axé sur les événements, et la limite supérieure anticipée pour atteindre 77 événements relatifs aux critères d'évaluation principaux sur 12 mois de suivi est de 452 patients. En résumé, l'objectif de cet essai bayésien multicentrique à répartition aléatoire est de comparer deux stratégies de prise en charge de patients présentant un BBG d'apparition récente après une IVAC, soit une approche guidée par une EEP, par rapport à une surveillance non invasive de 30 jours. Trial registration number: NCT03303612.

sudden cardiac death, and left ventricular systolic dysfunction.[9-11] The 2020 American College of Cardiology expert consensus report highlights the clinical equipoise between a strategy consisting of noninvasive monitoring vs a routine electrophysiological study (EPS) with permanent pacemaker implantation in the event of significant conduction disease.[12] Similarly, the 2021 European Society of Cardiology management guidelines state that either approach is currently acceptable in patients with new-onset LBBB after TAVI.[13] The aim of this **Co**mparison of a Clinical **M**onitoring Strategy Versus **E**lectrophysiology-Guided Algorithmic Approach in Patients With a New Left Bundle Branch Block After **TAVI** (COME-TAVI) trial is to perform a randomized head-to-head comparison of 2 clinical strategies: noninvasive monitoring vs a routine EPS with permanent pacemaker implantation for those with a His to ventricle (HV) interval $\geq$ 65 ms,[14] to determine the preferred approach to managing patients with new-onset persistent LBBB post-TAVI.

Methods and Analysis

Objectives

Primary endpoint. The COME-TAVI trial is a pragmatic trial designed to help support an intervention decision, consider all the eventual risks and benefits of an intervention, and be translated easily into delivery of care.[15] Its exploratory design tests complementary interventions conducted in strictly controlled, optimized settings. The primary outcome is composite and was selected to capture potential major consequences associated with both randomly allocated strategies in patients with new-onset LBBB post-TAVI over a 12-month follow-up period. The composite outcome consists of the following: (i) sudden cardiac death; (ii) syncope; (iii) AV conduction disorder requiring a pacemaker (for a class I or IIa indication); and (iv) acute and chronic pacemaker complications or severe EPS-related life-threatening complications. The

decision to implant a pacemaker is made at the discretion of the treating team, but to qualify as a primary endpoint, it must be determined, by the clinical event committee, to meet criteria for a class I or IIA pacemaker indication for an AV conduction disorder. Details of all such events will be reviewed carefully and presented.

Secondary endpoints. Secondary outcomes will include individual components of the primary composite outcome, along with the following:

- hospitalizations (all-cause and cardiovascular);
- emergency room visits;
- cost-effectiveness;
- death (all-cause and cardiovascular);
- all acute and chronic pacemaker or EPS complications; and
- symptomatic bradycardia (including sinus bradycardia) requiring pacemaker implantation.

An independent clinical events committee will classify all primary and secondary endpoint events, as well as all deaths and hospitalizations.

Inclusion and exclusion criteria

All study patients are required to have a clinically indicated TAVI for aortic stenosis, as determined by the local multidisciplinary heart valve team. The type of valve implanted is at the discretion of the treating team, a multidisciplinary heart team committee that includes a cardiac surgeon and interventional cardiologists.

Inclusion criteria consist of the following:

- age $\geq$ 18 years;
- provision of informed consent to participate; and
- persistent new-onset LBBB documented on a 12-lead electrocardiogram (ECG) at day 2 after TAVI implantation.

A subject with transient new-onset LBBB that is no longer present at the time of randomization will not be eligible. The subject can be randomized at any time during or after day 2 post-TAVI during the index hospitalization.

LBBB is defined as follows:

- QRS duration $>$ 120 ms;
- dominant S wave in V1;
- broad monophasic R wave in lateral leads (I, aVL, V5-V6); and
- absence of Q waves in lateral leads (I, V_5-V_6; small q waves are permitted in aVL).[16]

Exclusion criteria consist of the following:

- prior pacemaker or implantable cardioverter-defibrillator;
- preexisting right bundle branch block (RBBB) or LBBB (ie, prior to TAVI); and
- class I or IIA indication for pacemaker/implantable cardioverter-defibrillator implantation according to management guidelines.[16]

Protocol

Patients with new-onset LBBB post-TAVI who meet the inclusion criteria will be screened. Written consent will be obtained from interested participants. Patients will be randomized to either the EPS-guided strategy or 30-day continuous electrocardiographic monitoring through the DACIMA system (EvidentIQ, Montreal, QC) Figure 1. Randomization will initially be performed in a 1:1 ratio. The probability that a participant will be assigned to a given treatment arm will change over time, as efficacy information accumulates through the process of outcome-adaptive randomization. More specifically, the randomization ratio will be reassessed after each 10-unit increment in new primary endpoint events. This process is intended to maximize safety by decreasing the likelihood that trial participants will be exposed to the less-effective diagnostic strategy on the basis of accumulating evidence from the trial.[17]

Electrophysiology testing and pacemaker implantation. Electrophysiological testing will be performed with the patients under conscious sedation. Through femoral venous access, one 5-F quadripolar catheter will be advanced to record a His-bundle potential, and 10 HV interval measurements will be averaged. A permanent pacemaker will be implanted if the average HV interval is $\geq$ 65 ms.[14] In observation of the intention-to-treat principle, patients who develop a pacemaker indication after randomization will be analyzed according to their allocated treatment arm. If a pacemaker indication occurs prior to randomization, such patients will be excluded from the study. The pacemaker type and model will be determined at the discretion of the treating physician. In the setting of a low left ventricular ejection fraction (LVEF), cardiac resynchronization therapy and/or a cardioverter-defibrillator will be recommended, per management guidelines.[13,18] A pacemaker programming scheme (Table 1) will be suggested and encouraged, to maximize uniformity.

Transcutaneous cardiac monitoring. Transcutaneous cardiac patches (m-Health Solutions device, Hamilton, ON) will allow continuous electrocardiographic monitoring for a 30-day period. The PocketECG from m-Health is attached to 3 electrodes on the chest and contains a SIM card that transmits to a server located in Burlington, Ontario, Canada. In accordance with the standard of care, the COME-TAVI coordinating centre and the associated site will be informed rapidly if any of the following arrhythmic events occur:

- ventricular fibrillation;
- sustained ventricular tachycardia of $>$ 30 seconds;
- any RR interval $>$ 5 seconds; or
- third-degree AV block or Mobitz 2 second-degree AV block.

At the end of the 30-day period, the full report will be sent to the local principal investigator.

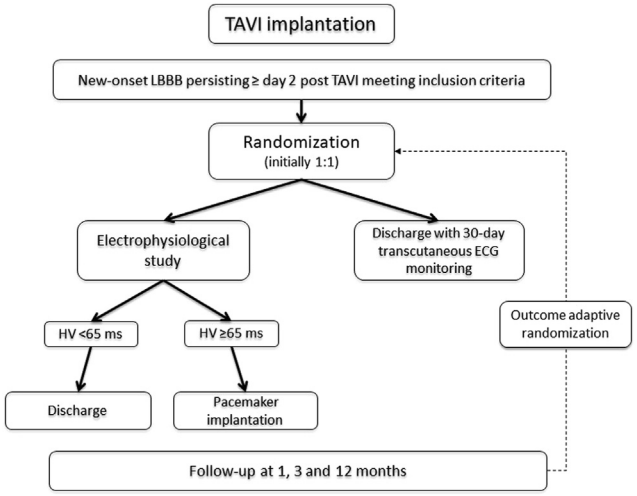

Figure 1. Flow diagram of the study. ECG, electrocardiogram; HV, His to ventricle interval; LBBB, left bundle branch block; TAVI, transcatheter aortic valve implantation.

Follow-up (flowchart)

The following data will be collected at baseline (Table 2):

- clinical examination (body mass index, blood pressure, New York Heart Association functional class, mini-mental state examination [MMSE] score); sex; ethnicity; clinical history (including tobacco use, history of atrial fibrillation or syncope, history of myocardial infarction; coronary artery bypass graft or other cardiac surgery; angioplasty; previous aortic valve dilation; vascular disease; cardiac risk factors; stroke/transient ischemic attack; chronic obstructive lung disease); quality of life (EuroQol-5D [EQ-5D)]; **Euro**pean **S**ystem for **C**ardiac **O**perative **R**isk **E**valuation (EuroSCORE) II;
- 12-lead ECG before TAVI (underlying rhythm; QRS morphology; heart rate [beats/min]; PR, QRS, RR, QT, and QTc interval durations [ms]);
- laboratory testing (B-type natriuretic peptide [BNP], glomerular filtration rate, hemoglobin, platelet count);
- transthoracic echocardiography (systolic/diastolic left ventricular (LV) volume; biplane LVEF; left ventricular end-diastolic pressure (LVEDP; normal vs elevated); diastolic dysfunction (grade); mitral regurgitation (grade); left ventricular outflow tract (LVOT) diameter; aortic annulus; aortic mean gradient; aortic peak velocity (Vmax); aortic calcifications; tricuspid regurgitation (grade); pulmonary artery pressure [PAP]);
- TAVI implantation (valve type and size; surgical approach route; position of the prosthesis; predilation balloon size; depth of the prosthesis in outflow tract; per-procedure complication; temporary pacemaker implantation);
- daily 12-lead ECG after TAVI until discharge (conduction disturbances: AV, intraventricular; heart rate (beats/min); PR, QRS, RR, QT, QTc interval durations (ms); evolution of conduction disturbances; supraventricular or ventricular rhythm disorders; time of onset and persistence of LBBB); and
- telemetry during hospitalization.

The following data will be collected at 3 and 12 months:

- 12-lead ECG; and
- pacemaker interrogation if applicable.

Table 1. Proposed pacemaker programming scheme

Company	Models	Recommended programming
For dual-chamber pacemakers		
Medtronic (Minneapolis, MN, USA)	Advisa Adapta Ensura	AAI-DDD 50−120 bpm (MVP) with rate response if indicated
Biotronik (Berlin, Germany)	Eluna Entovis Etrinsa Edora	DDD-ADI 50−120 bpm (Vp suppression) or DDD-IRS+ with CLS with rate response if indicated or CLS
Sorin Medical (New York, NY, USA)	Reply Kora	AAI-DDD 50−120 bpm (SafeR) with rate response if indicated
St. Jude Medical (now Abbott; Little Canada, NM, USA)	Accent Assurity Endurity	DDD 50−120 bpm VIP on (3 beats with max AV delay of 455 ms, every 30 s) with rate response if indicated
Boston Scientific (Marlborough, MA,USA)	Vitalio Altrua Accolade Ingenio Advantio Essentio	DDD 50−120 bpm Hysteresis on (AV search hysteresis +, max of 400 ms) with rate response if indicated
For single-chamber pacemakers		
All companies	All models	VVI 50 bpm with rate response if indicated

ADI, real mode communication from Biotronik to preserve atrioventricular conduction; AV, atrioventricular; bpm, beats per minute; CLS, closed-loop stimulation; MVP, managed ventricular pacing; VIP, ventricular intrinsic preference; Vp, ventricular pacing.

Table 2. Flowchart of the COME-TAVI study

	Post-TAVI procedure	Post-TAVI follow-up visits				
Visits	Selection visit (0–30 d)	1-mo call	3-mo pacemaker group	3-mocall	12-mo visit	Additional visits
Duration	60–90 min	5–10 min	60 min	5–10 min	60 min	60 min
Location	Pre-admission		Research (or by phone) and pacemaker clinic		Research (or by phone)	Research (or by phone) and pacemaker clinic
Patient informed consent	X					
Demographic data, medical history	X					
Electrocardiogram	X		X		X	X
Medication	X	X	X	X	X	X
Pacemaker verification			X		X (if applicable)	
Questions on adverse events			X	X	X	X
Questions on your health			X	X	X	X
Consultation of medical file	X	X	X	X	X	X

COME-TAVI, **Co**mparison of a Clinical **M**onitoring Strategy Versus **E**lectrophysiology-Guided Algorithmic Approach in Patients With a New LBBB After **TAVI**; TAVI, transcatheter aortic valve implantation.

The following data will be collected at 12 months:

- transthoracic echocardiography (LVEF); B-type natriuretic peptide; and mini-mental state examination score.

Statistical analysis

Sample size and power calculations. According to previous studies, the group randomized to 30-day monitoring will experience an estimated 22% rate of the combined endpoint during 12 months of follow-up: 21% will experience syncope, asymptomatic bradycardia requiring pacemaker implantation,[9,19] or an asymptomatic AV block, and 1% will suffer sudden cardiac death.[20] Similar estimates were obtained from the recent Ambulatory Electrocardiographic **M**onitoring for the Detection of High-Degree **A**trio-Ventricular Block in Patients With New-Onset Pe**r**sistent L**e**ft Bundle Branch Block After Transcatheter Aortic Valve Implantation (MARE) trial, which showed a 20% rate of severe bradycardia or high-degree AV block over a 12-month follow-up period in 103 patients with new-onset LBBB post-TAVI.[19] The hypothesized rate of the combined endpoint in the EPS-guided algorithmic treatment arm is estimated at 7.5% and includes the following components: 5% pacemaker complication (ie, complication rate [acute, delayed, or late] of 10% in the 50% of patients who require a pacemaker after an EPS) [21]; 2% new indication for a permanent pacemaker; and 0.5% sudden cardiac death.[9] In a recent prospective open-label study in which all patients with new-onset LBBB and delayed HV interval received a prophylactic pacemaker, the rate of major pacemaker complication was 4.3%, and 0.5% suffered cardiac death at 12-month follow-up.[22]

Although the final sample size in a Bayesian adaptive trial with interim stopping rules is not fixed, assuming a 1% per year true loss to follow-up, a total of 226 subjects per treatment arm (ie, total sample size of 452) would be required for a standard frequentist trial (1:1 randomization) in order to provide 80% power to detect a 45% relative reduction in the primary endpoint, assuming a 2-tailed alpha of 5%. This corresponds to a total of 77 primary endpoint events, which is the point at which trial enrollment will be stopped, given that this is an event-driven trial.

Primary efficacy analysis. The primary analysis is a Bayesian analysis of the composite primary endpoint. A binomial likelihood will be used for the number of events within each treatment arm. The analysis will consider the prior distribution to be noninformative (flat). The posterior probability of a relative risk (RR) below 1 will be used as the basis of decision-making.

Secondary analysis. The analysis of the secondary endpoints expressed as events (components of the primary endpoint taken individually, hospitalization, etc.) will be frequentist. For each of those secondary endpoints, time from randomization to first occurrence of the endpoint will be compared across the 2 treatment arms using a log-rank test, and Kaplan-Meier survival curves will be presented. The log-rank test

will be conducted at the 2-sided 0.05 significance level. Sex-stratified analyses will be performed for both primary and secondary analyses.

Economic analysis. We will perform an economic evaluation consisting of 2 components, as follows: (i) a comparison of healthcare resource utilization and costs across the 2 treatment arms of the COME-TAVI trial by intention-to-treat; and (ii) a cost-utility analysis from the Canadian health funder (payer) perspective. Medical resource use, including physician office visits, cardiac procedures/tests, frequency and duration of emergency room visits, and frequency and duration of hospitalizations will be calculated and compared by treatment arm.

Interim analyses. At 2 time points during the study, specifically when approximately 25% (20) and 50% of subjects (39) have reached a primary event, an efficacy interim analysis will be conducted by the independent Data Safety Monitoring Board (DSMB). At both time points, the DSMB will determine if the evidence of benefit is sufficient to stop the study for superiority of one treatment arm over the other. The superiority conclusion at the interim points requires a posterior probability of effectiveness (RR $<$ 1) of at least 99%. In the absence of superiority or safety concerns, recruitment will be stopped when a total of 77 endpoints is reached.

Potential challenges and limitations

Inherent risks are associated with both treatment strategies. In the EPS-guided strategy with prophylactic permanent pacemaker implantation if needed, patients could be subject to acute, delayed, or late complications related to the EPS or pacemaker. In the monitoring group, patients could suffer syncope, symptomatic bradycardia, or sudden cardiac death. All these potential safety risks will be closely followed by the the Data and Safety Monitoring Board (DSMB). Furthermore, with outcome-adaptive randomization, the likelihood that a participant will receive the most effective strategy will increase during the trial.

Recruitment can be challenging in this predominantly older population. The study will be extended to other sites within Canada and France if the recruitment target is not reached. As a pragmatic trial comparing 2 management strategies, prophylactic pacemaker implantation is an integral component of the EPS-guided arm if the HV interval is $\geq$ 65 ms. This protocol-driven, preemptive approach to pacemaker implantation is not currently a class I or IIA indication for pacemaker implantation and therefore is not considered a primary endpoint event. Any nonprophylactic pacemaker implantation for a conduction system disorder (class I or IIA indication) that occurs during follow-up qualifies as a primary endpoint in both treatment arms (ie, in patients with an HV $<$ 65 ms randomized to the EPS-guided strategy and in any patient randomized to monitoring). Defining a primary outcome on the basis of "harder" clinical endpoints such as cardiovascular mortality would be of interest but would require a far greater sample size. Of note, the same primary outcome was retained in the **S**yncope: **P**acing or **R**ecording **i**n **t**he **L**ater **Y**ears (SPRITELY) trial, funded by the Canadian Institutes of Health Research.[23]

Study committees

The COME-TAVI Study Executive Committee is composed of medical and scientific experts and was responsible for developing the protocol. This committee is also responsible for evaluating any changes in the clinical environment during the course of the trial that could impact assumptions underlying the original protocol design, and amending the protocol accordingly. The study steering committee is composed of the executive committee, along with the coordinators of each participating region. The DSMB is independent from clinical investigators and is responsible for formulating recommendations regarding whether the trial should be continued or stopped, based on safety considerations. The DSMB includes experienced cardiologists (electrophysiology and interventional cardiology) and epidemiology/biostatisticians with expertise in Bayesian trials. Elements that will be weighed include statistical proof of efficacy at the predetermined interim analysis points, safety concerns, and ethical and practical issues. A detailed description of the procedures, data flow, and meeting schedule of the DSMB will be maintained in a separate DSMB charter.

Registration, approval, and funding

The COME-TAVI trial must be approved by each participating centre's institutional review board/independent research ethics committee. This trial is registered at http://www.clinicaltrials.gov under the registration number NCT03303612. Enrollment has begun and is anticipated to be completed by January 2024, with study completion by January 2025. Five sites (Montreal Heart Institute, Montreal, Quebec; Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec; McMaster University Medical Centre, Hamilton, Ontario; Mazankowski Alberta Heart Institute, Edmonton, Alberta; and Hôpital Sacré-Coeur, Montreal, Quebec) are actively recruiting, and 3 sites are in the process of opening (Western University Hospital, London, Ontario; Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; and Centre Hospitalier Universitaire de Nantes, Nantes, France). The COME-TAVI trial is funded by the Heart and Stroke Foundation of Canada.

Discussion

The management of conduction disorders post-TAVI is a major challenge of growing importance, given the expanding indications for TAVI and the high prevalence of post-procedural electrocardiographic changes. Whereas patients who do not develop ECG changes within 1 hour of the procedure have been shown to be at low risk, those with new-onset LBBB are at higher risk of developing high-degree AV block.[10,24] Several factors have been associated with new-onset LBBB and pacemaker implantation post-TAVI. These include the following: diabetes mellitus; baseline conduction abnormalities; female sex; the presence of high calcium volume in the area below the left coronary cusp and the non-coronary

cusp; use of a self-expandable valve in preference to a balloon-expandable valve; depth of implant; valve size/annulus size; pre-dilation balloon valvuloplasty; and postimplant balloon dilation.[2,25–27] The 2020 American College of Cardiology Expert Consensus and the 2021 European Society of Cardiology management guidelines suggest that a noninvasive monitoring approach or an EPS-guided approach with pacemaker implantation in the event of infra-Hisian conduction disease both appear to be reasonable strategies in patients with new-onset LBBB, based on current best evidence.[12,13] Whether one of these approaches should be favoured over the other remains unclear.

The role of measurement of the HV interval to predict later AV block and guide pacemaker implantation has been reported in several retrospective and longitudinal studies, but it has never been assessed in the context of a randomized clinical trial.[14,22,28] Conduction defects can occur immediately during the procedure or at a later time point, owing to an inflammatory process or a mechanical effect of valve expansion.[29] If an HV interval is to be measured, ideally it should be done at least 48 hours after TAVI, because the HV interval delay peaks immediately after TAVI and may decrease thereafter.[30] The ideal HV threshold at which a permanent pacemaker should be recommended remains unclear. Published studies have reported their experience using cutoff values of 55, 65, and 70 ms.[14,24,31,32] In a retrospective cohort study of 75 consecutive pacemaker-free patients with a TAVI implanted at the Montreal Heart Institute, an HV interval $\geq$ 65 ms predicted AV block with 83.3% sensitivity and 81.6% specificity by receiver operating curve characteristic analysis.[14] In multivariable analyses, the HV interval post-TAVI also was independently associated with all-cause mortality. The largest longitudinal study by Massoulié et al. included 183 patients with persistent (ie, $\geq$ 24 hours) new-onset LBBB post-TAVI who underwent an EPS.[22] Patients deemed to be at high risk (ie, HV interval $\geq$ 70 ms) received a permanent pacemaker. Patients deemed to be at lower risk received an implantable loop recorder. After a follow-up period of 12 months, high-degree AV block was identified in 30.6% of subjects (N = 56), 53% (25 of 47) in the high-risk group and 23% (31 of 136) in the low-risk group. In multivariable analysis, an HV interval $\geq$ 70 ms was independently associated with the occurrence of a high-grade conduction disorder (subdistribution hazard ratio 2.4 (95% confidence interval 1.2-4.8), $P = 0.010$).

Conclusion

New-onset conduction abnormalities are the most frequent complications post-TAVI, with new-onset LBBB associated with a higher risk of developing high-degree AV block after hospital discharge. Therefore, the need is urgent to develop a management strategy that reliably identifies and protects the subgroup at highest risk, while minimizing the number of patients who receive unnecessary pacemakers. The COME-TAVI trial was designed to address this issue by comparing a noninvasive electrocardiographic monitoring approach to an EPS-guided strategy in the context of a multicentre, randomized, Bayesian trial in patients with new-onset LBBB post-TAVI.

Ethics Statement

The COME-TAVI trial has been approved by the Ethic board of the MHI (MP-33-2015-149) and by each participating centre's institutional review board/independent research ethics committee.

Patient Consent

Written informed consent will be obtained from all the patients before enrollment.

Funding Sources

Funding was provided by the Heart and Stroke Foundation of Canada, which had no involvement in this study.

Disclosures

L.R. reports research grants from Bayer Inc., the Heart and Stroke Foundation, Canadian Institutes of Health Research (CIHR), and FRQS (Fonds de Recherche Québec-Santé). B.A. reports research grants from Edwards LifeSciences, Medtronic, Laralab Inc., and FRQS. R.K. reports speaker fees from Medtronic, and proctoring, consulting, and speaker fees from Edwards Lifesciences. The other authors have no conflicts of interest to disclose.

References

1. Cribier A. Invention and uptake of TAVI over the first 20 years. Nat Rev Cardiol 2022;19:427-8.
2. Auffret V, Puri R, Urena M, et al. Conduction disturbances after transcatheter aortic valve replacement: current status and future perspectives. Circulation 2017;136:1049-69.
3. Kawashima T, Sato F. Visualizing anatomical evidences on atrioventricular conduction system for TAVI. Int J Cardiol 2014;174:1-6.
4. Nazif TM, Chen S, George I, et al. New-onset left bundle branch block after transcatheter aortic valve replacement is associated with adverse long-term clinical outcomes in intermediate-risk patients: an analysis from the PARTNER II trial. Eur Heart J 2019;40:2218-27.
5. Testa L, Latib A, De Marco F, et al. Clinical impact of persistent left bundle-branch block after transcatheter aortic valve implantation with CoreValve Revalving System. Circulation 2013;127:1300-7.
6. Houthuizen P, Van Garsse LA, Poels TT, et al. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. Circulation 2012;126:720-8.
7. Aktug Ö, Dohmen G, Brehmer K, et al. Incidence and predictors of left bundle branch block after transcatheter aortic valve implantation. Int J Cardiol 2012;160:26-30.
8. Nuis RJ, Van Mieghem NM, Schultz CJ, et al. Timing and potential mechanisms of new conduction abnormalities during the implantation of the Medtronic CoreValve System in patients with aortic stenosis. Eur Heart J 2011;32:2067-74.
9. Urena M, Mok M, Serra V, et al. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol 2012;60:1743-52.
10. Toggweiler S, Stortecky S, Holy E, et al. The electrocardiogram after transcatheter aortic valve replacement determines the risk for post-

procedural high-degree AV block and the need for telemetry monitoring. JACC Cardiovasc Interv 2016;9:1269-76.

11. Megaly M, Abraham B, Abdelsalam M, et al. Short- and long-term outcomes in patients with new-onset persistent left bundle branch block after transcatheter aortic valve replacement. Cardiovasc Revasc Med 2020;21:1299-304.

12. Lilly SM, Deshmukh AJ, Epstein AE, et al. 2020 ACC expert consensus decision pathway on management of conduction disturbances in patients undergoing transcatheter aortic valve replacement: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2020;76:2391-411.

13. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J 2021;42:3427-520.

14. Rivard L, Schram G, Asgar A, et al. Electrocardiographic and electrophysiological predictors of atrioventricular block after transcatheter aortic valve replacement. Heart Rhythm 2015;12:321-9.

15. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol 2009;62:464-75.

16. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;51:e1-62.

17. Wang MD. Sample size reestimation by Bayesian prediction. Biom J 2007;49:365-77.

18. Meguro K, Lellouche N, Teiger E. Cardiac resynchronization therapy improved heart failure after left bundle branch block during transcatheter aortic valve implantation. J Invasive Cardiol 2012;24:132-3.

19. Rodes-Cabau J, Urena M, Nombela-Franco L, et al. Arrhythmic burden as determined by ambulatory continuous cardiac monitoring in patients with new-onset persistent left bundle branch block following transcatheter aortic valve replacement: the MARE study. JACC Cardiovasc Interv 2018;11:1495-505.

20. Urena M, Webb JG, Cheema A, et al. Impact of new-onset persistent left bundle branch block on late clinical outcomes in patients undergoing transcatheter aortic valve implantation with a balloon-expandable valve. JACC Cardiovasc Interv 2014;7:128-36.

21. Udo EO, Zuithoff NP, van Hemel NM, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm 2012;9:728-35.

22. Massoullié G, Ploux S, Souteyrand G, et al. Incidence and management of atrioventricular conduction disorders in new-onset left bundle branch block after TAVI: a prospective multicenter study. Heart Rhythm 2023;20:699-706.

23. Sheldon R, Talajic M, Tang A, et al. Randomized pragmatic trial of pacemaker versus implantable cardiac monitor in syncope and bifascicular block. JACC Clin Electrophysiol 2022;8:239-48.

24. Akodad M, Aldhaheri E, Marin G, et al. Transcatheter aortic valve replacement performed with selective telemetry monitoring: a prospective study. Int J Cardiol 2021;330:158-63.

25. Mahajan S, Gupta R, Malik AH, et al. Predictors of permanent pacemaker insertion after TAVR: a systematic review and updated meta-analysis. J Cardiovasc Electrophysiol 2021;32:1411-20.

26. Yoon SH, Galo J, Amoah JK, et al. Permanent pacemaker insertion reduction and optimized temporary pacemaker management after contemporary transcatheter aortic valve implantation with self-expanding valves (from the Pristine TAVI study). Am J Cardiol 2022;189:1-10.

27. Wang T, Ou A, Xia P, et al. Predictors for the risk of permanent pacemaker implantation after transcatheter aortic valve replacement: a systematic review and meta-analysis. J Card Surg 2022;37:377-405.

28. Shin DI, Merx MW, Meyer C, et al. Baseline HV-interval predicts complete AV-block secondary to transcatheter aortic valve implantation. Acta Cardiol 2015;70:574-80.

29. Steinberg BA, Harrison JK, Frazier-Mills C, Hughes GC, Piccini JP. Cardiac conduction system disease after transcatheter aortic valve replacement. Am Heart J 2012;164:664-71.

30. Badenco N, Chong-Nguyen C, Maupain C, et al. Respective role of surface electrocardiogram and His bundle recordings to assess the risk of atrioventricular block after transcatheter aortic valve replacement. Int J Cardiol 2017;236:216-20.

31. Knecht S, Schaer B, Reichlin T, et al. Electrophysiology testing to stratify patients with left bundle branch block after transcatheter aortic valve implantation. J Am Heart Assoc 2020;9:e014446.

32. Tovia-Brodie O, Ben-Haim Y, Joffe E, et al. The value of electrophysiologic study in decision-making regarding the need for pacemaker implantation after TAVI. J Interv Card Electrophysiol 2017;48:121-30.