The Incidence, Predictors and Implications of Cardiac Conduction Abnormalities Following Transcatheter Aortic Valve Implantation (TAVI) to Treat Aortic Stenosis

Thesis with published works

Dr. Karan Rao

Submitted in fulfillment of the requirements for the degree of Doctor of Philosophy

The University of Sydney, Faculty of Medicine and Health

2026

ACKNOWLEDGEMENTS

As I reflect on my PhD journey, I am filled with gratitude for the encouragement and guidance I have received from many remarkable individuals. Each of you have played a pivotal role in my life, shaping not only my research but also my personal growth. This section serves as a heartfelt appreciation for those that have been influential during my PhD candidature.

I want to begin by expressing my profound gratitude to my parents, Mukesh and Priti, whose unconditional love and support have shaped who I am today. With a small suitcase, a few hundred dollars, and a dream of a better life, they arrived in Australia and immediately embodied hope and resilience for their two children. Their journey will always remain a constant source of inspiration and motivation. They instilled in me the values of hard work, discipline, and an unyielding passion for learning. From the very beginning, whilst prioritising my education, they ensured I developed as a well-rounded individual, and tirelessly persevered through financial and logistical challenges. I am so very grateful for their sacrifices and the invaluable lessons they imparted, which have been instrumental in my personal journey.

I am deeply grateful to my supervisor, Professor Ravinay Bhindi, for his insightful guidance and support throughout this journey. From the very first time I met you in 2020, I was immediately drawn to your effortless ability to constantly relate your academic research questions with your clinical practice. Since then, you've become far more than a PhD supervisor – you have been a mentor, philosopher and a friend. Ravi, you have instilled in me the importance of never standing still, always urging me to push boundaries and pursue work that makes a real difference. You have taught me to approach research with purpose, and to always challenge the status quo.

I would also like to extend my heartfelt thanks to the RNS Structural Team - the success of CONDUCT-TAVI was undoubtedly a collaborative effort. A special thank you to Dr. Peter Hansen

and Ms. Alex Baer, who have both been invaluable sounding boards for my ideas throughout. I am profoundly thankful to all my co-authors and collaborators for expanding my intellectual horizons throughout this journey, as well as to all the patients who participated in my research projects; without them, none of this would have been possible.

Last, but not least, I want to thank my beautiful wife, Heli. You have been my rock and my North Star since we were 16 years old, constantly compromising for our shared future. You've been my biggest cheerleader from the beginning, by celebrating all the wins along the way, but more importantly, supporting me through the numerous and inevitable troughs. Along with Kabir and Yuva, you have unknowingly taught me the essence of what truly matters. Kabir, your joyful spirit and curiosity serve as my constant motivation, reminding me to cherish the small moments and strive for a brighter future for you and your brother. Whilst Yuva joined our squad right at the end, he has seamlessly fit in as if he was always there. Together, you all inspire me to chase my ambitions with passion and determination, and without hesitation.

To all of you, and many more that I have not named, I am sincerely thankful for your contributions to my journey. Your love and encouragement have shaped my path and will continue to inspire me in all my future adventures.

AUTHOR ATTRIBUTION STATEMENTS

Chapter 2 of this thesis is published as:

Rao, K., Bhatia, K., Chan, B., Cowan, M., Saad, N., Baer, A., Sritharan, H., Bromhead, I., Whalley, D., Allahwala, U.K., Hansen, P. & Bhindi, R. (2022). 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. *BMJ Open*, 13(3).

This chapter is published work for which I was first author. I finalised the research protocol and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Chapter 3 is published as:

Rao, K., Chan, B., Baer, A., Hansen, P., & Bhindi, R. (2023). A systematic review of delayed high-grade atrioventricular block after transcatheter aortic valve implantation. *CJC Open*, 6(2). http://doi.org/10.1016/j.cjco.2023.10.003

This chapter is published work for which I was first author. I conceived and designed the study, collected and analysed the data, interpreted the findings, and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Chapter 4 is published as:

Rao, K., Ahmad, M., Brieger, D., Baer, A., Hansen, P., & Bhindi, R. (2025). Prognosis of new

bundle branch block after transcatheter aortic valve implantation. *Structural Heart.* 9 (3)

This chapter is published work for which I was first author. I conceived and designed the study, collected and analysed the data, interpreted the findings, and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Chapter 5 has been submitted for peer review. It is a large retrospective evaluation of the incidence and predictors of a new pacemaker after TAVI at our local institution. I am the primary author of this work, and was involved in the study conception, ethics, data-analysis and manuscript writing. Professor Ravinay Bhindi and co-authors provided intellectual input. I take primary responsibility for the accuracy and integrity of the work presented.

Chapter 6 is published as:

Rao, K., Chan, B., Bhatia, K., Saad, N., Baer, A., Whalley, D., Choong, C., Hansen, P. & Bhindi, R. (2025) Prospective observational study on the accuracy of predictors of permanent pacemaker secondary to high-grade atrioventricular conduction block after transcatheter aortic valve implantation (CONDUCT-TAVI). *Circulation: Cardiovascular Interventions.* Published online September 15th, 2025. DOI: https://doi.org/10.1161/CIRCINTERVENTIONS.125.015446

This is the primary prospective study of my PhD. I was involved in ethics submission and subsequent amendments. I then carried out consent and recruitment for all patients (200). During their procedure, I conducted the electrophysiology study and analysed dedicated imaging scans. Post-procedure, I inserted implantable loop recorders in all relevant patients and then organised and performed periodic follow up for all participants. I collected the data, performed all statistical analyses and interpretation. I also wrote the final manuscript. Professor Ravinay Bhindi and co-

authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Chapter 7 has been submitted for publication and is currently under peer review. I was the first author involved with the conceptualisation of the study as a post-hoc analysis of CONDUCT-TAVI. I primarily performed the data collection, analysis, follow up and manuscript writing. I am grateful for our collaboration with Professor Shlomo Ben-Haim and Professor Justin Tretter from Hobart Healthcare (London, United Kingdom) for additional analyses based on their uniquely developed and previously validated CT-A methods for estimating the conduction system pathway, including the atrioventricular node, Bundle of His and origin of the left bundle branch.

Chapter 8 has also been submitted for publication and is currently under peer review. I was the lead author involved in the conceptualisation of the study as post-hoc analyses of CONDUCT-TAVI. I assisted with data collection, analysis, cardiac segmentation and manuscript writing. Initially, this study was proposed as a post-hoc analysis reviewing demographic, electrical, anatomical and procedural predictors of NOAF, which was a secondary outcome from the prospective study detailed in Chapter 6 (CONDUCT-TAVI). The study then developed into a detailed volumetric and geometric evaluation of the left atrium using both traditional and machine-learning based methods for measurement. The manuscript includes a locally created mathematically derived algorithm for statistical shape analysis, which was created in collaboration with Dr. Daniel Han and his team at the School of Mathematics and Statistics at the University of New South Wales.

Chapter 9 of this thesis is currently under peer review. It includes work for which I am co-first author (along with Dr. Jonathan Ciofani). Along with Dr. Ciofani, I co-conceived and co-designed the study concept. I collected, analysed and interpreted the clinical aspects of the data, whilst Dr. Ciofani was primarily involved in the Mendelian randomization analyses. I led the drafting and

finalisation of the manuscript. The other co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Chapter 10 is published as:

Rao, K., Baer, A., Bapat, V., Piazza, N., Hansen, P., Prendergast, B., & Bhindi, R. (2024). Lifetime management considerations to optimize transcatheter aortic valve implantation: a practical guide. *EuroIntervention*, 20(24).

As first author I conceived the key ideas of the review and drafted the concepts in the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Chapter 11 is published as:

Rao, K., Litkouhi, P.N., Baer, A., Hansen, P. & Bhindi, R. (2025) Feasibility of same day discharge after transcatheter aortic valve implantation: Retrospective evaluation of the North Shore Day Stay TAVI Clinical Pathway. *Heart and Vessels.* Published online September 22, 2025, ahead of print. DOI: 10.1007/s00380-025-02598-4

This chapter includes work that has been published, for which I was co-first author. I conceived and designed the study, collected and analysed the data (along with my co-first author Dr. Neila Litkouhi), interpreted the findings, and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented. It is a retrospective post-hoc analysis on data collected as part of CONDUCT-TAVI (Chapter 7).

Chapter 12 is published as:

Rao, K., Baer, A., Hansen, P., & Bhindi, R. (2023). Recurrent valve frame infolding in the 34mm self-expanding Medtronic Evolut Pro+ transcatheter valve system: a single-centre experience. *Heart, Lung & Circulation*, 32(12).

This chapter is published work for which I was first author. I assisted in the design and conception of the study, and collected and analysed the data, interpreted the findings, and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

I confirm that the Author Attribution Statements are true and accurate.

PUBLICATIONS ARISING FROM THIS THESIS

This thesis is presented for examination as a thesis containing published work. At the time of submission, 7 of the chapters presented in this thesis have been published, whilst a further 4 chapters have been submitted and are under peer review at the time of thesis submission. The candidate is the principal (or co-principal where specified) author of each of these papers which have been arranged chronologically below.

Published at time of submission:

1. **Rao, K**., Bhatia, K., Chan, B., Cowan, M., Saad, N., Baer, A., Sritharan, H., Bromhead, I., Whalley, D., Allahwala, U.K., Hansen, P. & Bhindi, R. (2022). 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. BMJ Open. 13(3).

2. **Rao, K**., Baer, A., Hansen, P. & Bhindi, R. (2023) Recurrent valve frame infolding in the 34mm self-expanding Medtronic Evolut Pro+ transcatheter valve system: a single centre experience. Heart, Lung & Circulation. 32 (12)

3. **Rao, K**., Chan, B., Baer, A., Hansen, P. & Bhindi, R. (2023) A systematic review of delayed high grade atrioventricular block after transcatheter aortic valve implantation. CJC Open; 6 (2)

4. **Rao, K**., Baer, A., Bapat, V., Piazza, N., Hansen, P., Prendergast, B. & Bhindi, R. (2024) Lifetime management considerations to optimize transcatheter aortic valve implantation: a practical guide. EuroIntervention; 20 (24).

5. **Rao, K**., Ahmad, M., Brieger, D., Baer, A., Hansen, P. & Bhindi, R. (2025) Prognosis of new bundle branch block after transcatheter aortic valve implantation. Structural Heart Journal. 9 (3)

6. **Rao, K**., Chan, B., Bhatia, K., Saad, N., Baer, A., Whalley, D., Choong, C., Hansen, P. & Bhindi, R. (2025) Prospective observational study on the accuracy of predictors of permanent pacemaker secondary to high-grade atrioventricular conduction block after transcatheter aortic valve implantation (CONDUCT-TAVI). Circulation: Cardiovascular Interventions. Published online September 15th, 2025, ahead of print. DOI: https://doi.org/10.1161/CIRCINTERVENTIONS.125.015446

7. **Rao, K**., Litkouhi, P.N., Baer, A., Hansen, P. & Bhindi, R. (2025) Feasibility of same day discharge after transcatheter aortic valve implantation: Retrospective evaluation of the North Shore Day Stay TAVI Clinical Pathway. *Heart and Vessels.* Published online September 22, 2025, ahead of print. Currently in press. DOI: 10.1007/s00380-025-02598-4

Under peer review at time of thesis submission:

1. **Rao, K.,** Tretter, J.T., Asyraf, T., Spaziani, S., Bhindi, R. & Ben-Haim, S. (2025) Enhanced Prediction of Pacemaker Implantation Post-TAVI Using Pre-Procedural CTA, ECG, Device Characteristics, and Fluoroscopic Implant Depth. *Submitted for peer review.*

2. **Rao, K.** Baer, A., Hansen, P. & Bhindi, R. (2025) Retrospective single-centre study evaluating ECG and procedural predictors of new permanent pacemaker and left bundle branch block after transcatheter aortic valve implantation. *Submitted for peer review.*

3. **Rao, K.,** Han, D., Ciofani, J. C., Ahmed, M., Daniel, J.B., Saad, N., Baer, A., Hansen, P. & Bhindi, R. (2025) Combining clinical, anatomical, procedural and novel machine learning methods to predict new-onset atrial fibrillation at 1-year after TAVI. *Submitted for peer review.*

4. **Rao, K**., Ciofani, J.C., Han, D., Nazarzadeh, M., Rahimi, K., Baer, A., Saad, N., Litkouhi, P.N., Allahwala, U., Hansen, P. & Bhindi, R. (2025) The influence of calcific aortic stenosis on atrioventricular conduction: insights from CONDUCT-TAVI and Mendelian randomization analyses. *Submitted for peer review.*

PUBLICATIONS DURING PHD CANDIDATURE NOT INCLUDED IN THIS THESIS

1. **Rao, K**., Granger, E., Dvir, D. & Fahmy, P. (2022) BASILICA technique for prevention of coronary artery occlusion in high risk native transcatheter aortic valve replacement. Canadian Journal of Cardiology, 38 (8). DOI: https://doi.org/10.1016/j.cjca.2022.02.011

2. **Rao, K**., Brieger, D., Nour, D., Allum, J., Baer, A., & Bhindi, R. (2022) Cardiovascular Disease in Australians experiencing Homelessness. Heart, Lung and Circulation. 31 (12). DOI: https://doi.org/10.1016/j.hlc.2022.08.017

3. Litkouhi, N., **Rao, K.,** Baer, A., Hansen, P. & Bhindi, R. (2024) Aortic valve and left ventricular outflow tract calcium distribution and conduction outcomes after TAVI: a systematic review and meta-analysis. Structural Heart Journal. 9 (4) DOI: 10.1016/j.shj.2024.100389

4. Brieger, D., **Rao, K.,** Baer, A., Choong, C., Anastasias, M., Mahoney, P., Hansen, P. & Bhindi, R. (2024) Transcaval TAVI with left coronary artery BASILICA in high-risk symptomatic severe aortic stenosis. CJC Open. 7 (1) DOI: 10.1016/j.cjco.2024.09.018

5. Brieger, D., **Rao, K**., Nagaraja, V., Bhindi, R. & Allahwala, U. (2025) The use of glycoprotein IIB/IIIa inhibitors in elective PCI – A systematic review and meta-analysis of randomised trials. Vascular Pharmacology*, 159:* 107500. DOI: 10.1016/j.vph.2025/107500

6. Litkouhi, N., **Rao, K.,** Baer, A., Hansen, P. & Bhindi, R. (2025) The safety and feasibility of same day discharge for patients undergoing transcatheter aortic valve replacement: a systematic review and meta-analysis. Canadian Journal of Cardiology. *Online ahead of print.* DOI: 10.1016/j.cjca.2025.05.007

STATEMENT ON THE USE OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

Generative AI tools were not used in this thesis. Reference management software (Endnote Version 21.0) was used to semi-automate referencing throughout the thesis.

AUSTRALIAN GOVERNMENT SUPPORT STATEMENT

This research was supported by an Australian Government Research Training Program (RTP) Fee Offset. The thesis works were also supported via a National Health and Medical Research Council (NHMRC) PhD Scholarship and Heart Research Australia PhD Scholarship.

PRESENTATIONS ARISING FROM THIS THESIS

Rao, K. (2025) Prospective observational study to evaluate the incidence and predictors of permanent pacemaker implantation at 1 year after TAVI (CONDUCT-TAVI).

CSANZ Ralph Reader Clinical Prize Session. August 2025. Brisbane, Australia.

Rao, K. (2024) Prospective observational study to evaluate the incidence and predictors of permanent pacemaker implantation at 1 year after TAVI (CONDUCT-TAVI), Preliminary results.

ANZET Early Career Research Prize Session. August 2024. Perth, Australia.

Rao, K. (2024) Prospective observational study to evaluate the incidence and predictors of permanent pacemaker implantation at 1 year after TAVI (CONDUCT-TAVI), Preliminary Results.

First Prize. Kolling Institute Sydney University Annual Research Forum. November 2024. Sydney, Australia.

Rao, K. (2024) Prospective observational study to evaluate the incidence and predictors of permanent pacemaker implantation at 1 year after TAVI (CONDUCT-TAVI).

Oral presentation. PCR London Valves December 2024. London, United Kingdom.

Rao, K. (2024) Prognosis of bundle branch block after TAVI.

Oral presentation. PCR London Valves December 2024. London, United Kingdom.

Rao, K. Ciofani, J. Rahimi K., Nazarzadeh, M…Hansen, P. & Bhindi, R. (2024) The influence of calcific aortic stenosis on atrioventricular conduction: a combined observational and Mendelian Randomization study.

Oral Presentation. PCR Tokyo Valves February 2024. Tokyo, Japan.

Rao, K., Saad, N., Baer, A., Hansen, P. & Bhindi, R. (2024) Predicting acute and delayed pacemaker implantation in patients with preexisting RBBB undergoing TAVI.

Oral presentation. PCR Tokyo Valves February 2024. Tokyo, Japan.

Rao, K., Chan, B., Baer, A., Hansen, P. & Bhindi, R. (2023) The incidence of delayed high-grade atrioventricular block after TAVI: A systematic review of 15626 patients.

Mini-oral presentation. Cardiac Society of Australia New Zealand (CSANZ). August 2023. Adelaide, Australia.

Rao, K. (2022) Minimalist TAVR: Managing conduction disturbance. *China Valve (Hangzhou) 2022 Conference.* Invited lecture.

Oral presentation. **China Valves Conference April 2022.** *Presented Online.*

Rao, K. (2022 & 2024) High-grade AV block after TAVI. *Medtronic TAVI Summit.* Invited lecture.

Oral presentation – March 2022, March 2024

AWARDS, PRIZES, SCHOLARSHIPS AND GRANTS WON DURING PHD CANDIDATURE

- **Ralph Reader Clinical Prize Winner**
    - Cardiac Society of Australia New Zealand (CSANZ), August 2025. Brisbane, Australia.
    - *Prospective observational study to evaluate the incidence and predictors of new permanent pacemaker implantation at 1-year after TAVI (CONDUCT-TAVI).*

- **First Prize, Early Career Research Award**
    - Australia and New Zealand Endovascular Therapies Conference (ANZET) August 2024. Perth, Australia.
    - *Prospective observational study to evaluate the incidence and predictors of new permanent pacemaker implantation at 1-year after TAVI (CONDUCT-TAVI): Preliminary results.*

- **First Prize** Kolling Institute Annual Research Symposium. Best Oral presentation. November 2024. Sydney, Australia.
    - *Prospective observational study to evaluate the incidence and predictors of new permanent pacemaker implantation at 1-year after TAVI (CONDUCT-TAVI): Preliminary results.*

- **National Health and Medical Research Council (NHMRC) PhD Scholarship Recipient** (2023-2024). $100,000

- **Heart Research Australia (HROz) PhD Scholarship Recipient** (2023-2024). $60,000, including $10,000 for research consumables.

Other scholarships:

1. Royal North Shore Staff Student Council Travel Scholarship (2022), $3000. London Valves 2022.
2. BIOTRONIK Travel Fellowship (2024), $1000.

Grants:

1. Prospective study to assess suitability of same-day discharge following transcatheter aortic valve implantation
    a. Medtronic: $51,600 (2023) for research consumables
2. Optimising outcomes of transcatheter aortic valve implantation
    a. Heart Research Australia: $80,000 (2024-2025)
3. Randomised Control Trial to assess the utility of an extended wearable rhythm monitor device (CONDUCT-TAVI II)
    a. Heart Research Australia: $80,000 (2025-2026)

LIST OF COMMON ABBREVIATIONS

AF: atrial fibrillation

AH Interval: Atrial-His Interval

AS: aortic stenosis

AV: atrioventricular

AVW: atrioventricular Wenckebach

BAV: balloon aortic valvuloplasty

BEV: balloon-expandable valve

CABG: coronary artery bypass graft

CAD: coronary artery disease

CHB: complete heart block

CI: confidence interval

CT: computed tomography

ECG: electrocardiography

EPS: electrophysiology study

eGFR: estimated glomerular filtration rate

HGAVB: high grade atrioventricular block

HV Interval: His-Ventricular Interval

LBBB: left bundle branch block

LCA: left coronary artery

LCC: left coronary cusp

LVEF: left ventricular ejection fraction

MSL: membranous septum length

NOAF: new onset atrial fibrillation (after TAVI)

NCC: non-coronary cusp

NYHA: New York Heart Association

OR: odds ratio

PPM: patient prosthesis mismatch

PPMI or PPI: permanent pacemaker implantation

PVL: paravalvular leak

RAP: rapid atrial pacing

RBBB: right bundle branch block

RCA: right coronary artery

RCC: right coronary cusp

SAVR: surgical aortic valve replacement

SEV: self-expanding valve

STJ: sinotubular junction

STS: Society of Thoracic Surgeons

TAVI: transcatheter aortic valve implantation

TAVR: transcatheter aortic valve replacement

THV: transcatheter heart valve

Table of Contents

SECTION I: INTRODUCTION

CHAPTER 1: Literature Review, Aims and Overview of Thesis

1.1 Aortic stenosis and its association with the cardiac conduction system

The aortic valve regulates blood flow from the left ventricle into the ascending aorta, and in most cases, comprises of three leaflets. Aortic stenosis (AS) refers to the narrowing of the aortic valve, which most commonly occurs secondary to degenerative calcification. The restriction of valve leaflets can limit the outflow of blood (cardiac output), and when severe, AS has an untreated mortality of 50% at 5-years(1). The prevalence of AS globally increases exponentially with age, and in Australia, the prevalence is 1.5% over the age of 55 years, and 3.5% over the age of 75 years(2). In younger patients (under 55 years), the leading cause is bicuspid aortic valve disease, an uncommon congenital heart condition affecting approximately 0.5-0.8% of the population, in which individuals are born with two aortic leaflets instead of three. Aside from these, traditional cardiometabolic risk factors such as dyslipidaemia, obesity, hypertension, diabetes and chronic kidney disease have been associated with a greater prevalence of aortic stenosis in retrospective studies(3-7).

The most common presentations of aortic stenosis include chest pain, dyspnoea or syncope, however rarely it may result in sudden cardiac death, reported in up to 9.2% of symptomatic patients at 5 years(8). This has been attributed to reduced cardiac output, concomitant coronary disease, tachyarrhythmias, and perhaps most commonly – unrecognised bradyarrhythmia. It has been historically believed that calcific aortic stenosis is associated with impaired atrioventricular and intraventricular conduction, however this understanding is based primarily off small single centre studies from the mid to late 20th century.

The cardiac conduction system involves the passage of the action potential from the atrium into the ventricle in a streamlined and synchronized manner, facilitating rapid myocyte depolarisation and contraction. More specifically, spontaneous depolarisation occurs at the

sinoatrial (SA) node in the right atrium, which then triggers a cascade resulting in atrial depolarisation. This then funnels into the atrioventricular (AV) node, which is anatomically located at the apex of the Triangle of Koch, bordered by the Tendon of Todaro posteriorly, the ostium of the coronary sinus basally, and the septal aspect of the tricuspid valve annulus anteriorly (Figure 1). Here, the fibres concentrate into to the Bundle of His, which comprises of three sections. The first is the *penetrating* bundle which enters the central fibrous body (located between the left and right atrium, and adjacent to the aortic root). After this, it becomes the *non-branching* bundle, which then emerges from the fibrous body, within the membranous septum, as the *branching* bundle. It is here that the Bundle of His bifurcates into the left and right bundle branches, which depolarise in a synchronised manner to coordinate ventricular contraction.

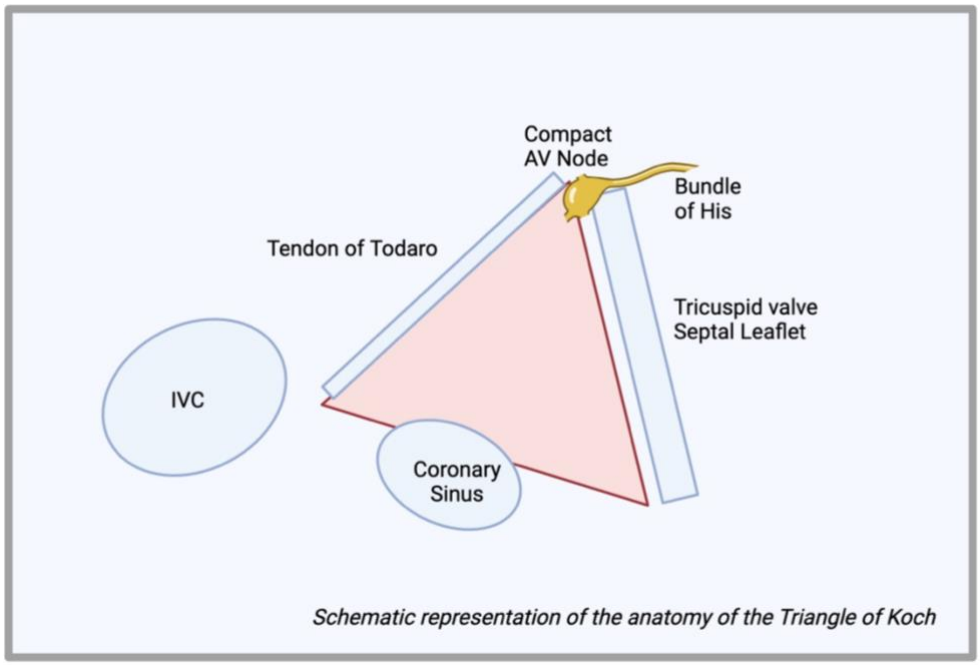

Figure 1: Schematic representation of the anatomy of the Triangle of Koch
IVC: inferior vena cava, AV: atrioventricular

Yater & Cornell first described the association between conduction disease and calcific aortic stenosis in 1935, using histopathological models in 11 patients with calcific AS and complete AV block(9). The authors were able to demonstrate that the conduction system was damaged

adjacent to calcium in all patients, and due to either “invasion” of calcium in nine patients, or via fibrosis secondary to compression by calcium in the other four patients. Importantly, they reported normal conduction proximal and distal to the regions of calcium and noted calcium masses extended typically from the aortic leaflet into the interventricular septum towards the junction of the membranous and muscular septum. Subsequently, multiple retrospective ECG studies have shown a high prevalence (26-90%) of conduction deficits such as left axis deviation, bundle branch block and atrioventricular block in patients with aortic stenosis, and uniformly also suggesting a greater prevalence in calcific AS phenotypes(10, 11).

The introduction of invasive electrophysiology studies in 1967 helped further shape understanding with better localisation of conduction disease. In 1977, Dhingra *et al.*(12) conducted electrophysiology studies on 32 patients with AS. Of these, 8 (25%) were found to have complete atrioventricular block, whereby the conduction block was located Hisian or Infra-Hisian in all 8 patients, and all patients had highly calcific degenerative AS. In the remaining 24 patients with intact atrioventricular conduction, the authors reported prolonged His-Ventricular conduction (HV) in patients with more calcific anatomy and higher valve gradients. In 1978, Friedman *et al*.(13) compared 26 consecutive patients with symptomatic aortic valve disease (stenosis or regurgitation) to control patients without valvular pathology. In AS, patients had prolonged HV interval compared to controls, with no difference in PR and AH interval. In aortic regurgitation, the site of disease was supra-Hisian, with prolonged AH and PR intervals compared to controls, and no difference in the HV interval.

Since then, there is a notably paucity in studies investigating the incidence of conduction disease in patients with aortic stenosis. This is despite the availability of computed tomography (CT) and magnetic resonance imaging (MRI) allowing for improved spatial

resolution and detailed volumetric quantification of aortic valve calcium. Furthermore, compared to these historical studies, typical patient populations are now older, with greater comorbidities, suggesting our current understandings of the natural history of conduction in aortic stenosis may be outdated. The most relevant contemporary study was published in 2015, which monitored 435 patients with aortic stenosis for a day *prior* to their transcatheter aortic valve implantation (TAVI). The authors found the incidence of *incidental* high-grade atrioventricular block was 5.5%. Whilst the focus of contemporary work is now almost entirely on post-intervention (TAVI or surgical aortic valve replacement) conduction disease, an updated and improved understanding of the natural history of conduction in aortic stenosis can help shape future research in the field.

1.2 Transcatheter aortic valve implantation as a treatment for aortic stenosis and other expanding indications

Historically, the sole definitive treatment of AS has been surgical aortic valve replacement (SAVR), involving an open-heart procedure with cardiopulmonary bypass. The procedure typically involves excision of the diseased native leaflets, which are then replaced by either a bioprosthetic or metallic aortic valve that is sutured at the level of the native annulus. The safety and success of SAVR has varied based on patient age, co-morbidities, clinical status and anatomy. Risk scores such as the Society of Thoracic Surgeons - Predicted Risk of Mortality (STS-PROM)(14) and EuroScore II(15) have been prospectively validated to classify patients into low, intermediate and high surgical risk categories based off predicted in-hospital and 30-day outcomes. TAVI was first developed as a minimally invasive alternative treatment for patients of high or prohibitive surgical risk. It was first performed on April 16th, 2002, by Dr. Alain G. Cribier in Paris, France, in a 57-year-old male with symptomatic severe aortic stenosis in cardiogenic shock.

Since 2002, the use of TAVI has exponentially increased, and this transformation has been driven by advances in valve technology, pre-procedural planning, implant techniques, and robust evidence from a series of randomised control trials. The original PARTNER I studies (2010, 2011) demonstrated balloon-expandable TAVI to be non-inferior to SAVR in high surgical risk patients, and superior to medical therapy in inoperable patients(16, 17). The CoreValve study followed in 2014, demonstrating non-inferiority of the self-expandable platform against SAVR in high surgical risk patients(18). The subsequent PARTNER II and SURTAVI trials demonstrated non-inferiority of balloon-expandable and self-expanding prostheses against SAVR in patients of intermediate surgical risk(19, 20). Most recently, the PARTNER III study demonstrated *superiority* of TAVI against SAVR with respect to death, stroke or rehospitalisation at 1 year, and sustained non-inferiority at mid-term (5 year) follow up(21). The Evolut Low Risk trial, the self-expanding valve equivalent study, showed non-inferiority to SAVR with respect to death or disabling stroke, also sustained to 4 years of follow up(22). The NOTION study is the only prospective randomised trial to assess the long-term durability of TAVI beyond this period. Their recently published 10-year follow up results demonstrated that the self-expanding TAVI platform was non-inferior to SAVR with respect to all-cause mortality, stroke, myocardial infarction, and bioprosthetic valve failure. However, the study's generalisability has been questioned due to its relatively small sample size and exclusive use of self-expanding valves across three hospitals in Denmark and Sweden(23).

Major international guidelines have now incorporated the evidence into treatment recommendations for AS. The most recent American College of Cardiology/American Heart Association guidelines recommend TAVI for patients aged over 80 years and suggest shared decision making to determine the choice between TAVI and surgical aortic valve replacement

(SAVR) in those aged 65 – 80 years(24). In contrast, the 2025 European Society of Cardiology/European Association of Cardiothoracic Surgery (ESC/EACTS) guidelines suggest TAVI in patients aged 70 years or more and SAVR in younger patients at low surgical risk (or bicuspid valve disease), with shared decision making in other patients according to clinical, anatomical and procedural factors (25). In 2019, TAVI overtook SAVR in the United States of America as the most performed treatment for aortic stenosis(26), and Australia followed this pattern in 2021.

An important consideration when interpreting the randomised evidence to date is its applicability to populations which were notably underrepresented. Both the PARTNER III and Evolut Low Risk trials excluded patients with hostile or "prohibitive" annular anatomies, which resulted in almost complete exclusion of bicuspid aortic valve disease. TAVI in bicuspid anatomies poses a unique challenge due to multiple factors. Firstly, sizing is often more complex due to large and often elliptical annular geometry which may be outside standard prosthesis reference ranges. Secondly, the aortic apparatus (annulus to leaflets) may be flared or tapered (non-tubular) in many patients, which increases the risk of under- or over-sizing if using annular measurements alone. Thirdly, bicuspid anatomies are often more calcified than tricuspid anatomies and may involve rigid and calcified raphe resulting in asymmetric prosthesis expansion, increasing the risk of annular rupture, paravalvular leak and conduction abnormalities(27). While the variations in bicuspid anatomies can significantly affect procedural success, current data indicates that TAVI performs comparably in carefully selected patients(28). Conversely, the outcomes in surgery remain excellent in bicuspid patients, with mortality ranging from 0.9-2.4%, although these results are drawn primarily from young patients with very low surgical risk(29, 30).

The use of TAVI may also soon extend beyond severe symptomatic AS. The EARLY-TAVR study demonstrated that TAVI performed earlier in the disease course, in *asymptomatic* severe AS patients outperformed clinical surveillance with respect to death, stroke or unplanned rehospitalisation(31).However, contrastingly, the TAVR-UNLOAD found no benefit of early intervention with TAVI against clinical surveillance in patients with moderate AS and heart failure with reduced ejection fraction (HFrEF)(32), although this study was self-admittedly underpowered. TAVI is also being investigated for the treatment of pure native aortic valve regurgitation (AR). Currently the use is limited to inoperable or high-surgical risk patients and involves the off-label use of currently available devices. However, these devices have significant anchoring challenges due to the absence of calcification in AR anatomies. This often necessitates greater prosthetic oversizing to prevent valve embolization, which has been associated with higher rates of annular rupture and conduction disturbances. While off-label use of these platforms has demonstrated acceptable outcomes in inoperable or high-risk patients, the overall results remain inferior to those observed in AS cohorts. However, newer dedicated devices utilizing leaflet-clipping anchoring mechanisms have shown significantly improved performance and may help to expand the role of TAVI in the management of pure AR(33).

1.3 High-grade atrioventricular block and left bundle branch block after transcatheter aortic valve implantation

High-grade atrioventricular block (HGAVB) refers specifically to second-degree Mobitz II and complete (third-degree) heart block and may arise from either primary (degenerative) or secondary causes, such as myocardial infarction or valvular intervention. Assessing the temporal trends and precise prevalence of primary HGAVB is challenging due to the lack of comprehensive, contemporary population-based studies. However, the overall prevalence in the community was estimated at approximately 0.02-0.04%, based on a study conducted in

1965 in the United States(34). In a more recent cohort study that tracked patients over 17 years, key clinical and demographic factors associated with high-grade atrioventricular block included age (HR 2.23 per decade), male sex, diabetes, and chronic kidney disease(35).

Whilst patients with AS may potentially have an elevated risk of cardiac conduction disease even without intervention, it is well established that any valvular intervention significantly *increases* the risk, although it appears to be particularly amplified after TAVI. In contemporary low surgical risk cohorts, the incidence of a new pacemaker at 30-days after SAVR was 4.1-6.1%, whereas after TAVI it was noted in 6.6-17.4%(36, 37). During TAVI, a transcatheter heart valve (THV) is placed within the aortic valve apparatus, in the so called "*device landing zone"* (DLZ). The DLZ refers to a region comprising the aortic leaflets, aortic annulus and a short segment of the left ventricular outflow tract (LVOT) (Figure 2). The sub-valvular component of the DLZ borders the membranous septum, which harbours the non-branching and branching segments of the Bundle of His, as well as the superficial left bundle branch. Contrasting to SAVR, the native diseased valve leaflets are not excised during TAVI – instead the THV splints the diseased leaflets open. For this reason, THVs are commonly oversized between 5-15% to the annular measurement, as they rely on radial force for calcium-based anchoring rather than most surgical valves which utilise suture-based anchoring. This leaves the conduction system more vulnerable to mechanical injury after TAVI. If the Bundle of His is irrevocably damaged, it may result in partial or complete atrial and ventricular electrical dissociation (high-grade atrioventricular block), which often requires treatment with a permanent pacemaker implantation. If left untreated, high-degree HGAVB may cause syncope, cardiac arrest, and even death. If only the superficial left bundle branch is damaged, this manifests as a left bundle branch block (LBBB), associated with

cardiac dyssynchrony thereby increasing the risk of cardiomyopathy and future bradyarrhythmia.

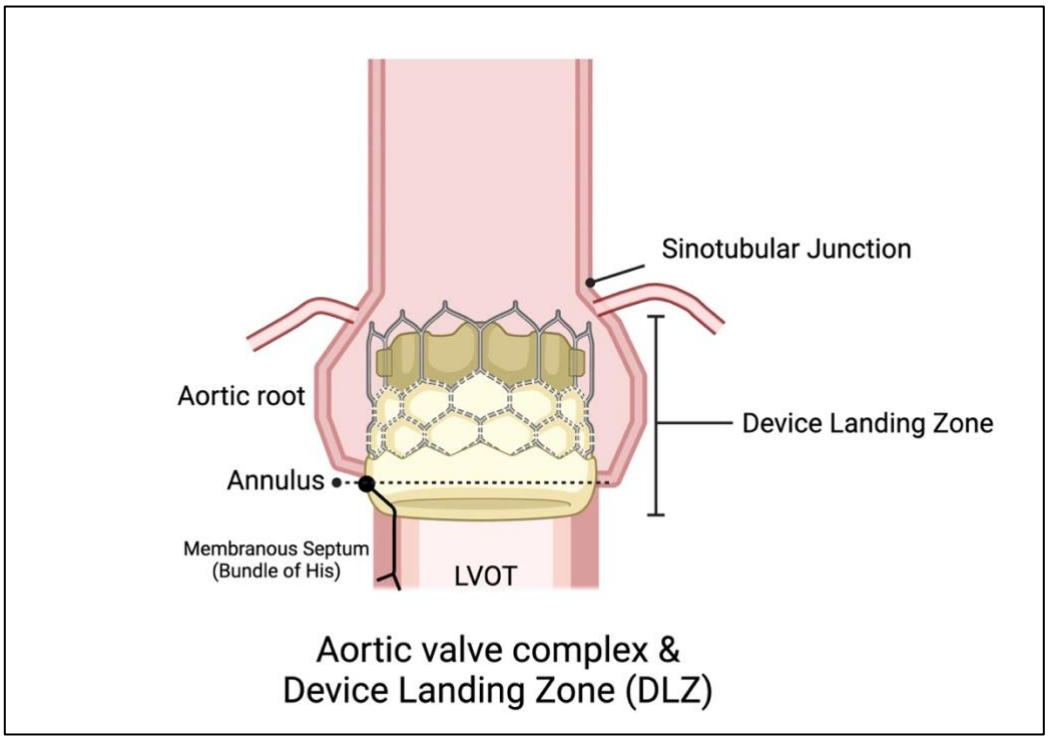

Figure 2: Relevant aortic root anatomy and structures during TAVI.
LVOT: left ventricular outflow tract

Iatrogenic heart block after TAVI most commonly occurs *early*, within the first 48 hours, due to immediate mechanical disruption of the conduction pathway, either directly via an implanted THV, or indirectly via calcium translocation. Notably however, a substantial proportion may occur *late*, after 48 hours, which can be challenging to promptly identify and treat. The aetiology for the late presentation of HGAVB is less understood and may be a combination of persisting valve-related injury (inflammation) and progressive conduction disease. Nevertheless, it carries serious clinical implications considering unexplained sudden cardiac death after TAVI has often been attributed to bradyarrhythmia and makes up 7.5% of all deaths at 2-years post TAVI (38).

Similarly, the incidence of a new *persistent* LBBB is estimated at 20% after TAVI(39, 40). Whilst initially considered a benign outcome, it is now believed that persistent LBBB after TAVI should be avoided, if possible, due to an associated increase in mortality, heart failure related rehospitalisation and delayed pacemaker requirements at extended follow up(41).

There are a variety of complementary factors which influence the likelihood of conduction disease after TAVI, including patient anatomy, pre-existing cardiac conduction disease, as well as procedural factors such as implantation depth and valve design which are discussed further in Section 1.4. Precise and reliable prediction of HGAVB remains of high clinical priority, considering optimal risk stratification can help guide post-procedural monitoring and earlier treatment of potentially vulnerable patients. Improved identification of primary risk factors may also tailor valve selection and implantation depth to mitigate risk of PPMI, given emerging data indicating higher long-term all-cause and cardiovascular mortality in patients requiring PPMI (42). Additionally, a better understanding of the risk of early and late conduction abnormalities can facilitate rapid streamlining of low-risk patients suitable for same or next-day discharge after TAVI.

1.4 Published risk factors of high-grade atrioventricular block and new left bundle branch block after transcatheter aortic valve implantation

A variety of demographic, anatomical, procedural, and electrophysiological factors contribute to the development of HGAVB and new onset LBBB after TAVI, which underscores the complexity in predicting its occurrence.

Demographic Factors

Advancing age is a recognized risk factor for the increased occurrence of degenerative conduction disease and is also linked to a higher likelihood of post-procedure pacemaker requirement(43). Additionally, male gender, higher body mass index (BMI), type 2 diabetes mellitus, and chronic kidney disease have also been associated with a greater need for PPMI following TAVI (43-45).

Anatomical Factors

Specific anatomical characteristics may amplify the mechanical interaction between THVs and the native cardiac conduction pathway, correlating with increased post-procedural PPMI risk. It is known that the Bundle of His traverses the membranous septum and emerges at its inferior (ventricular) aspect prior to bifurcating into the left and right bundle branches. Therefore, the membranous septum length (MSL), which can be reliably measured on pre-procedure CT, has emerged as an anatomical surrogate to estimate risk of post-procedural conduction disease(46). CT-based infra-annular MSL measurement demonstrates fair reproducibility, and a shortened MSL predicts pacemaker risk, whereas conversely a longer MSL may be protective (46-48). Whilst various methods for MSL measurement exist, a reproducible technique described by Jilaihawi *et al.* (49) involves placing the crosshair between the non and right coronary cusp on an axial view of the aortic root in an

appropriately gated systolic-phase image to isolate the inter-leaflet triangle and visualise the membranous septum on the stretched-vessel plane (Figure 3). One of the criticisms of this approach has been a failure to incorporate the mean length across the width of the membranous septum (rotating anterior to posterior), thus resulting in a potentially high error margin. A Danish group have published significant differences in MSL depending on the location – measurements under the right coronary cusp (anterior) were found to be up to 2.5mm shorter (closer to the annulus) compared to the non-coronary cusp (posterior)(48). More recently, Tretter *et al.* have proposed averaging the MSL across its width by incorporating an anterior (representing the origin of the LBBB) and posterior measurement (representing the emergence of the bundle of His), which may serve as a more reproducible method moving forward(50). Hokken *et al.* identified a length less than 3mm as the highest risk for pacemaker(46), however a reliance on absolute measurements alone may be flawed, as they fail to account for patient and device related factors.

Morphological variations in the membranous septum may also be influential – and specifically two other variants of the His have been described, both with potential ramifications. The first (affecting 30% of individuals) was described by Kawashima and Sasaki in 2005(51) and may be protective since the His bundle is shielded, as it extends inferiorly into the muscular ventricular septum. In contrast, the second less common variation (affecting 20%) may result in a perilously *exposed* His traversing under a thin layer of sub-endocardium in the membranous septum – the so called "naked" His bundle. Variation in the circumferential rotation of the membranous septum may also theoretically alter the risk conduction system injury(52) by altering the course of the Bundle of His relative to the implanted prosthesis, although this has yet to be studied formally in a post-TAVI cohort.

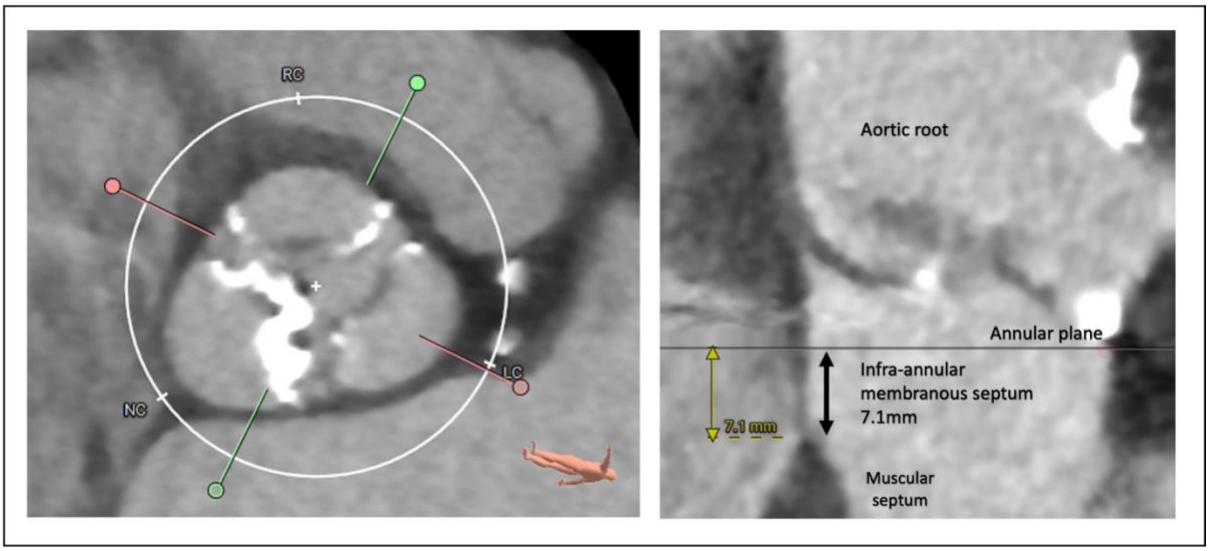

Figure 3: Identification and measurement of the infra-annular membranous septum using the methods described by Jilaihawi et al. (2019) (49).

Left: axial view of the aortic root showing three leaflets with a crosshair between the non-coronary cusp and right coronary cusp.
Right: corresponding "stretched vessel" view demonstrating the inter-leaflet triangle and infra-annular membranous septum.

Previously published work has also suggested that elevated aortic root calcification volume correlates with higher incidence of pacemaker implantation(53). The impact of cusp-specific calcium volume remains controversial with conflicting findings regarding the highest risk distribution(54-56). The reasons behind this discordance may relate to varying aetiologies for calcium-mediated conduction disease. One proposed hypothesis is that elevated calcium burden in the non-coronary or right coronary cusps may cause direct conduction system trauma post-THV deployment, given the proximity to the Bundle of His. An alternative hypothesis is that left coronary cusp calcification may have a stronger correlation due to asymmetric THV expansion directed toward the conduction system.

Procedural Factors

Procedural factors are equally influential in determining the likelihood of PPMI. The use of mechanically expanding valves and self-expanding valves have historically been associated

with a higher incidence of HGAVB, compared to balloon-expandable platforms. This has been attributed to greater radial force, a deeper implant and generally greater annular and LVOT oversizing(57). This was particularly magnified in the now recalled mechanically expanding Boston Scientific Lotus System which was engineered to have high radial force and prolonged delivery time with constant contact with the LVOT. This resulted in a 35.3% incidence of new PPMI at 30 days, compared to 19.1% in the self-expanding valve arm of the REPRISE III randomised clinical trial(58). Similarly, annular oversizing greater than 20%, irrespective of valve design, has also been shown to further amplify the interaction between the prosthesis frame and the conduction system, and sharply increase the risk of post-procedural conduction disease(59, 60).

Depth of implantation has also been published to correlate with pacemaker risk. A deeper implant alludes to a more ventricularly displaced deployment and increases the likelihood of interaction with the exposed Bundle of His and left-bundle branch, thereby increasing the risk of post-procedural conduction disease (Figure 4). However, the concept of tailoring the implantation depth to the patient's anatomy was proposed by Jilaihawi *et al.* in 2019(49). The authors demonstrated that pacemaker risk in their cohort peaked when the implant depth exceeded the patient's MSL, whereas the absolute value of the implant depth and MSL were less predictive. However, it should be noted that estimating the implant depth has historically relied fluoroscopy, which may be flawed considering the substantial risk of foreshortening and parallax, especially in the traditional three-cusp implantation view. This may also explain why measured implant depths differed when measured using post-procedure CT aortography, compared to fluoroscopy, with CT-based measurements having a stronger association with PPMI risk(61).

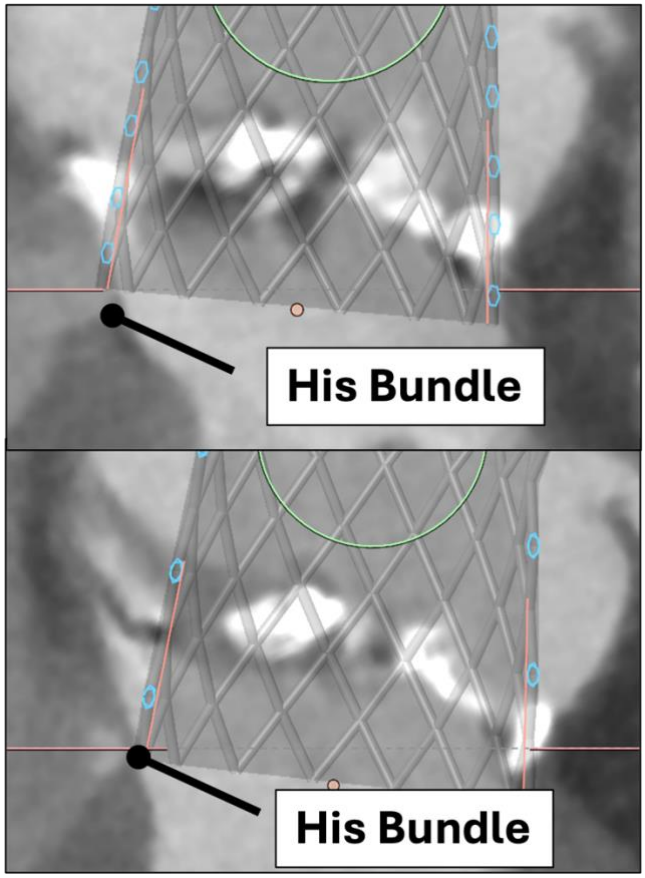

Figure 4: The influence of depth of implantation on interaction with the conduction pathway.
The top image shows a "high" simulated implant depth which does not interact with the exposed His bundle at the inferior margin of the membranous septum. The bottom image shows a "deeper" simulated implant on the same patient demonstrating interaction with the exposed His bundle.

More recently, the introduction of the cusp-overlap technique(62) has reduced pacemaker rates following self-expanding valve deployment. This approach emphasizes initial valve positioning in a two-cusp fluoroscopic projection, specifically designed to *isolate* the non-coronary cusp through deliberate overlap of the left and right coronary cusps. This angle facilitates anatomical elongation of the LVOT (and thus membranous septum) and reduces the risk of foreshortening. The use of the comparatively stiffer Lunderquist wire is believed to provide further structural support for precise depth control. Using these methods, and also

with the introduction of annular markers (dots) at the valve inflow, there has been a shift towards *higher* implant depths, which likely accounts for the temporal trend towards reduction in PPMI rates. Parallel developments in balloon-expandable valve procedures, particularly the High Implantation Technique utilizing the "lucent line" approach(63) to achieve an aortic to ventricular implant ratio of 95:5 or 90:10 has similarly resulted in improved conduction outcomes(64). However, consideration must be given to the implications of higher implantations on future TAVI-in-TAVI feasibility, particularly pertinent given the increasing application of TAVI in younger, healthier patient populations. Subsequent TAVI-in-TAVI procedures will result in pinning of the index TAVI leaflets, thereby establishing a risk plane through the formation of an extended "neo-skirt" or "tube-graft" configuration. Thus, while higher implantation depths may reduce pacemaker necessity, these benefits must be balanced against implications on coronary re-access.

More recently, studies have used novel computer simulation software to predict future THV force on the LVOT (maximum contact pressure) and the proportional area subjected to that force (contact pressure index) with good correlation between these indices and the likelihood of pacemaker implantation(65). Furthermore, left ventricular outflow tract tapering or calcified bicuspid valve morphology may also promote prosthesis-induced mechanical injury of the Bundle of His resulting in higher rates of PPMI.

Electrophysiology Factors

Various electrophysiological parameters have been identified as having strong associations with post-procedure conduction abnormalities. Most notably, a baseline RBBB has been most strongly associated with high-grade atrioventricular block, due to the common incidence of periprocedural His Bundle or left bundle branch injury. Other baseline conduction

disturbances associated with post-TAVI PPMI include atrial fibrillation, first and second degree atrioventricular block, and fascicular block, alluding to reduced conduction system reserve in these patients(66). Periprocedural transient high-grade atrioventricular block, post-procedural prolongation of the PR or QRS interval or the development of a new LBBB has also been associated with PPMI(67).

Recently, periprocedural electrophysiological studies (EPS) have been proposed as a valuable method for near field and dynamic assessment of conduction system integrity. The His-Ventricle (HV) interval serves as a sensitive marker of infra-Hisian conduction, while rapid atrial pacing to induce AV Wenckebach (Mobitz Type I) enables functional assessment of the AV-His-Ventricular axis. In 2015, Rivard *et al.(68)* demonstrated that a post-TAVI HV interval exceeding 13 milliseconds (ms) was associated with a higher risk of PPMI. Additionally, a HV interval greater than 65 ms in patients with a new-onset LBBB was shown to predict delayed HGAVB following TAVI(40). Similarly, rapid atrial pacing induced AV Wenckebach performed immediately after TAVI was also reported to be associated with PPMI by Krishnaswamy *et al.* in 2019(69).

Despite the identification of numerous multimodal risk factors, a reliable predictive algorithm for PPMI following TAVI remains elusive. To date, research has mostly focused on individual predictors rather than their combined effects, which is problematic since these factors may confound one another. Additionally, the literature is biased toward early outcomes (in-hospital PPMI or PPMI within 30 days), whilst delayed PPMI and late arrhythmic events remain understudied. Furthermore, most studies to date have relied on clinical presentations, intermittent ECG recordings, or standard follow-up appointments, to identify post-procedure arrhythmias rather than continuous rhythm monitoring, which may underestimate the

incidence of subclinical arrhythmias that may still carry clinical significance. Therefore, comprehensive studies that simultaneously evaluate anatomical, procedural, and electrophysiological determinants, and that incorporate extended continuous rhythm monitoring, are essential to develop more accurate and reliable predictive models which can ultimately optimise patient care.

1.5 New-onset atrial fibrillation after transcatheter aortic valve implantation

Atrial fibrillation is one of the most prevalent tachyarrhythmias in the developed world, and has been strongly associated with increasing age, with a lifetime risk of 37% in patients over 55 years(70). Modifiable risk factors with a strong association include body mass index, hypertension, diabetes mellitus, obstructive sleep apnoea, myocardial infarction, heart failure, and smoking history(71). Post cardiac surgery, the incidence of new in-hospital atrial fibrillation has been observed to be notably higher, estimated at 42.6%, and within this context, has been associated with adverse outcomes including prolonged hospital admission, permanent pacemaker implantation, stroke and transition to persistent AF(72).

The incidence of NOAF after cardiac surgery has been attributed to physiological stress and inflammation of the procedure, mechanical manipulation of the heart, alterations in autonomic nervous tone, fluctuations in fluid balance and disruption in levels of adrenaline. In contrast, NOAF after TAVI does not appear to be as common, with a systematic review published by Ryan *et al.* reporting an incidence of 10% at 30 days(73). The mechanisms of NOAF after TAVI are unclear, although it may share some parallels with cardiac surgery. However, the literature to date suggests that NOAF after TAVI shares similarly unfavourable outcomes, including increased post-procedure mortality, stroke, rehospitalisation and pacemaker rates(73). Despite these implications, there have been few studies that have

investigated NOAF through continuous rhythm monitoring, allowing capture of both clinical and subclinical episodes. A recently published study was one of the first to use continuous rhythm monitoring, albeit for only 14 days, to document the incidence of device-detected NOAF at 7.0%(74). Similarly, another recent study used implantable loop recorders to monitor patients with a new LBBB after TAVI and found the incidence of NOAF was 29% at 2-years, and notably, the majority were subclinical episodes.

Similar to high-grade atrioventricular block after TAVI, there are no reliable prediction algorithms for NOAF. A large meta-analysis(73) suggested NOAF was more common in older patients, those with transapical access (as opposed to transfemoral), and those with chronic kidney disease, peripheral vascular disease, severe mitral regurgitation and a higher STS derived surgical risk score. Valve type, aortic root anatomy, chronic obstructive pulmonary disease (COPD) and diabetes were notably *not* associated with NOAF incidence.

Prospective studies that incorporate extended continuous rhythm monitoring are needed to more precisely define the risk and predictors of NOAF after TAVI. Improved detection of subclinical and late-presenting NOAF would help to clarify its contribution to post-TAVI stroke, especially those presenting after the first 48 hours, and would provide an evidence base for future work to determine whether anticoagulation for brief or asymptomatic episodes yields clinical benefit in this particularly high risk (post-TAVI) cohort, with elevated thromboembolic and bleeding risk.

1.6 Aims

Specifically, the aims of this thesis are:

- To understand the incidence and timing of high-grade atrioventricular block leading to permanent pacemaker implantation at 1-year following TAVI
- To comprehensively evaluate demographic, anatomical, electrophysiological and procedural predictors of high-grade atrioventricular block leading to permanent pacemaker implantation at 1-year following TAVI
- To understand the incidence and prognosis of new-persistent left bundle branch block after TAVI
- To understand the incidence and predictors of clinical, and subclinical, new onset atrial fibrillation at 1-year following TAVI
- To explore broader procedural and management issues for TAVI as a treatment for aortic stenosis, which includes:
    - Key considerations in the lifetime management of aortic stenosis managed with TAVI
    - Safety and feasibility of achieving same-day discharge after TAVI

1.7 Overview of thesis

TAVI serves as an effective intervention for patients with symptomatic aortic stenosis, providing a minimally invasive alternative to SAVR. TAVI involves percutaneously deploying a bioprosthetic valve through peripheral vascular access, leading to improved haemodynamics, enhanced quality of life, and reduced mortality in appropriately selected patients. Section I begins as an introduction to TAVI as a treatment for aortic stenosis, followed by a literature review on the incidence, predictors and implications of procedure-related conduction abnormalities. Section I ends with a published research protocol which covers the methodology of the primary prospective study included in this thesis.

Section II explores the incidence, predictors and clinical implications of high-grade atrioventricular block and bundle branch block after TAVI, through a series of systematic reviews, meta-analyses, retrospective studies, and culminating with a large prospective observational study (CONDUCT-TAVI).

Section III of the thesis builds upon the comprehensive CONDUCT-TAVI study through three targeted post-hoc analyses, which together aim to 1) enhance pacemaker risk prediction; 2) explore the association between TAVI and new-onset AF, and 3) reevaluate assumptions about the relationships among aortic stenosis, TAVI, and arrhythmias.

Whilst initially TAVI was limited to patients at prohibitive or high surgical risk, it has since expanded to include individuals across all surgical risk levels, resulting in treatment for younger and healthier patients. This shift necessitates a comprehensive approach to lifetime management of aortic stenosis, ensuring that follow-up and treatment plans are tailored to each patient's evolving health needs. Section IV begins with a published *Expert Review* on

the lifetime management considerations for patients treated with TAVI. Moreover, improvements in procedural techniques and valve designs, coupled with rising hospital demands, have prompted earlier discharges post-TAVI. The safety and feasibility of same-day discharge is also explored in Section IV.

With the uptake in TAVI and rapidly broadening patient eligibility, dedicated research is needed to improve our understanding of post-TAVI arrhythmias, optimise lifetime management, and shift towards safer and earlier post-procedure discharge.

CHAPTER 2: Methods

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

Open access Protocol

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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 Rao ,[1,2,3] 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,[1,3] Ravinay Bhindi[1,2,3]

Published in:

BMJ Open 2023 Vol. 13 Issue 3 Pages e070219

Author contribution statement:

This chapter is published work for which I was first author. I finalised the research protocol and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Note:
The study was initially designed for two-year follow up, however the research protocol and ethics were amended in 2022 to 1-year follow up following consultation with the research team. This manuscript was accepted for publication prior to the ethics amendment and protocol update, and thus still includes the initial 2-year follow up research protocol.

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 Rao[1,2,3], Kunwardeep Bhatia[1], Bernard Chan[1,3], Mitchell Cowan[1,2], Natasha Saad[1,2], Alexandra Baer[2], Hari Sritharan[1], Ingrid Bromhead[1], David Whalley[1, 2, 3], Usaid Allahwala[1, 2, 3] Peter Hansen[1,2] & Ravinay Bhindi[1,2,3]

[1] Royal North Shore Hospital, Sydney, NSW, Australia

[2] North Shore Private Hospital, Sydney, NSW, Australia

[3] The University of Sydney, Sydney, NSW, Australia

Corresponding author:

Professor Ravinay Bhindi

Royal North Shore Hospital, Reserve Road, St. Leonards, 2065.

Email: ravinay.bhindi@sydney.edu.au

Acknowledgements:

The trial is self-funded by the Royal North Shore Cardiology Department, with implantable loop recorders provided in good faith by BIOTRONIK (Berlin, Germany)

Grant number: FF 074

2.1.1 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 (HGAVB) 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, multi-centre, 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 computed tomography (CT) measurements, 12-lead electrocardiography, valve characteristics, percentage oversizing, and implantation depth. Follow up will be for two 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.

Keywords: aortic stenosis, TAVI, transcatheter aortic valve implantation, conduction, atrioventricular block, pacemaker, electrophysiology study

Strengths and limitations of the study

- This study has broad inclusion criteria which increases the generalisability of the results
- This study utilises 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

2.1.2 Introduction

Aortic stenosis (AS) is the most common cardiac valve pathology, and often manifests with the classical triad of dyspnoea, angina, and syncope(2). 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(2). 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 (75, 76). The American Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy

(STS/ACC TVT) registry data confirms frequency of TAVI has now surpassed surgical aortic valve replacements since 2019(26), and Australia is also following a similar trend. In 2021, the cost of TAVI in Australia was estimated at $53, 164, based on an average hospital stay of 6 days(77). With TAVI approved for low-risk patients(78), 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(79-81). 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 (47, 53, 80, 82). 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 (83). 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

two years (84). 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 (85). 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 (86). 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.

2.1.3 Study Rationale

Currently, there is no accurate algorithm to identify patients likely to develop HGAVB after TAVI. Similarly, procedural predictors of AF following TAVI are not well understood. Right atrial pacing has been shown to be a sensitive, but not a specific test to predict HGAVB after TAVI (69). Krishnaswamy et al. (69) demonstrated that patients who do not exhibit right atrial pacing induced atrioventricular (AV) block at a cycle length ≥ 500ms (AV Wenckebach cycle length) 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 right atrial pacing to predict HGAVB could be improved by performing it both prior to and immediately after TAVI. We hypothesize that patients who develop a significant change to the cycle length 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 right atrial 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 (68, 87). However, its added utility over right atrial 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".

2.1.4 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 computed tomography (CT), 12 lead electrocardiography (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 two years after TAVI. The study protocol is also published and available on the Australia and New Zealand clinical trials

registry [Trial Number ACTRN12621001700820]. 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 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 (eighteen) 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 clinic 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.

Computed tomography (CT) analysis

Prior to TAVI, all patients undergo pre-procedure ECG-gated multidetector computer tomography (MDCT). 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, mm3)
- Coronary cusp (left, right and non-coronary) upper, basal and 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 (88). The membranous septum will be measured using a previously published technique(89), 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 transfemoral venous access will be obtained for passage of the multi-electrode electrophysiology catheter (BIOTRONIK, Berlin, Germany).

Both centres utilise two transcatheter heart valves, the balloon-expandable Sapien 3 system (Edwards Lifesciences, 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 utilising the Cusp Overlap technique(90) for the self-expandable platform and the High Deployment Technique(63) for the balloon-expandable platform Following implantation, the implantation depth (mm) will be measured on co-planar 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 day 3-5 based on clinical discretion. Discharge timing is not mandated by the study protocol.

ECG analysis

All patients will undergo 12-Lead electrocardiograms (ECG) using standard methodology at the following timepoints: Immediately before and after TAVI, 4 hours post TAVI, 24 hours post TAVI, 28 days post TAVI, and 6-, 12- and 24-months post TAVI. All patients will undergo rapid right atrial pacing and HV interval measurements immediately before and after TAVI.

Rapid right atrial pacing

Right atrial (RA) pacing will be performed immediately before valve deployment, and then immediately after deployment, using a multi-electrode 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. (69), where RA pacing was incremented by 10 beats per minute (bpm) from 70bpm - 120bpm 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 70bpm 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 1000ms (or 60ms above the patients resting cycle length). The pacing cycle length should be progressively shortened by 10ms decrements every 3 beats until AV Wenckebach occurs or until a maximum cycle length of 400ms 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 right atrial pacing performed.

Measurement of HV interval

The HV interval will be measured using the same multi-electrode 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 (± 2ms) over at least 3 beats. The multi-electrode catheter will be removed at the end of the procedure. If there is a clinical indication for continued pacing (for example transient or complete heart block), this multi-electrode 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 beats per minute, tachycardia

above 180 beats per minute, pauses over 3 seconds, 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 peri-operative complete heart block or Mobitz II second degree heart block are managed with a permanent pacemaker. The exact indication for insertion and time from 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. Firstly, RA pacing and AV Wenckebach results: 50ms increase in AV Wenckebach cycle length (CL) after TAVI, 50ms increase in AV Wenckebach CL AND 13ms increase in HV interval after TAVI, and absolute AV Wenckebach CL ≥500ms immediately before and/or after TAVI. Secondly, related to the HV interval results: 13ms increase in HV interval after TAVI, and absolute HV interval post TAVI >65 milliseconds. Electrocardiography (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, atrial fibrillation, 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 cycle length after TAVI (ms)
- Percentage change in AV Wenckebach cycle length after TAVI (%)
- Change in HV interval after TAVI (ms)
- AV Wenckebach cycle length after TAVI (ms)
- AV Wenckebach cycle length prior to TAVI (ms)
- HV interval after TAVI (ms)
- HV interval before TAVI (ms)
- Noncoronary cusp device-landing zone calcium volume (NCC-DLZ CA) (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 (RAO-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, 24 months

We also aim to determine the proportion of patients that develop new atrial fibrillation 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, 24 months

Prespecified subgroup analysis will be conducted by:

- valve type (balloon expanding or self-expanding transcatheter heart valve)
- presence of atrial fibrillation or flutter immediately prior to TAVI
- presence of atrial fibrillation 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 two years to be 15%. A sample size of 194 produces a two-sided 95% confidence interval 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 drop-out rate of 5%, a total enrolment sample size of 205 patients is required.

Analysis

For each pre-specified 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 (AUROC) will also be calculated for pre-defined 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 Northern Sydney Local Health District (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 for the form 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 Centre 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 Organisation 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 Northern Sydney Local Health District (NSLHD) Human Research Ethics Committee (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 two 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 minutes, due to the targeted EP study, and loop recorder implantation. Despite the added procedural time, we hypothesize 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.

2.1.5 Significance

HGAVB 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 HGAVB 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. Whilst there are various known risk factors for HGAVB, 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 HGAVB, which is monitored via an implantable loop recorder for a period of two years. The results of this study will improve our prediction algorithm for HGAVB and pacemakers, and as such, help to streamline and optimise TAVI, reduce hospital lengths of stay, and most importantly, improve patient outcomes.

2.1.6 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.

Author Contributions

KR, KB, BC, MC, NS, AB, HS, IB, DW, UA, 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.

Competing interests

The authors have no competing interests or disclosures. CONDUCT-TAVI is self-funded by the Royal North Shore Cardiology Department. The implantable loop recorders which will be used in the trial are provided in good faith by BIOTRONIK (Berlin, Germany).

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 *FF 074*. 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.

2.1.7 Figures and Tables

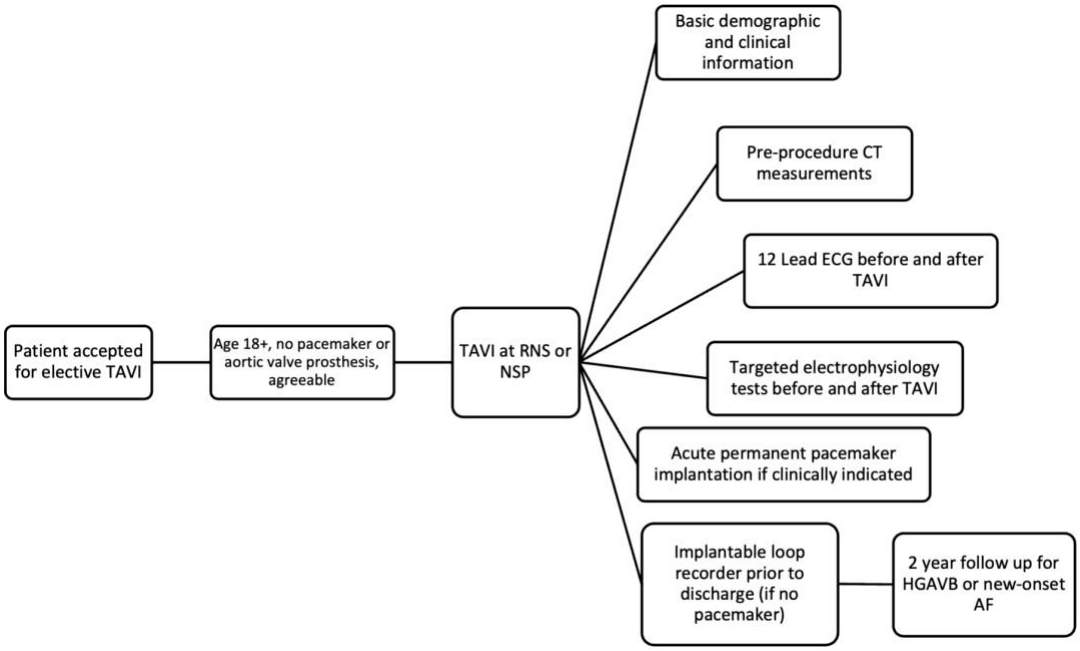

Figure 1: Summary of CONDUCT-TAVI protocol.

AF, atrial fibrillation; HGAVB, high-grade atrioventricular conduction block; NSP, North Shore Private Hospital; RNS, Royal North Shore Public Hospital; TAVI, transcatheter aortic valve implantation.

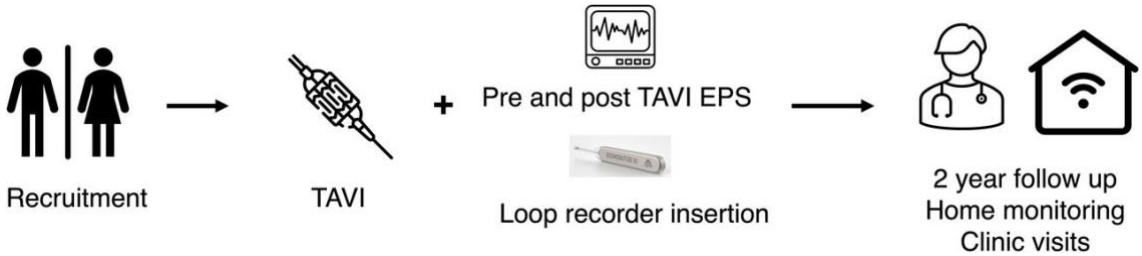

Figure 2: CONDUCT-TAVI trial focus on pre and post TAVI electrophysiology study and loop recorder insertion, with 2 years planned follow-up via home monitoring and clinical visits.

EPS, electrophysiology study; TAVI, transcatheter aortic valve implantation.

Schedule	**Admission for TAVI**	**Post-TAVI Visits (28 days, 6 months, 12 months and 24 months after TAVI)**
Informed Consent	✓	
Inclusion / Exclusion criteria	✓	
Demographics	✓	
Medical History	✓	✓
Medications List	✓	✓
Height, Weight, Vital Signs	✓	
Electrocardiogram	✓	✓
Transthoracic Echocardiogram	✓	✓ (28 days, 12 months, and 24 months only)
Rapid Atrial Pacing	✓	
Measurement of HV Interval	✓	
Loop recorder implantation	✓	
Loop recorder or PPM interrogation		✓
Adverse Event & Serious Adverse Event Assessment	✓	✓

Table 1: CONDUCT-TAVI patient schedule

SECTION II: TAVI AND THE CARDIAC CONDUCTION SYSTEM

CHAPTER 3: A systematic review of delayed high-grade atrioventricular block after transcatheter aortic valve implantation

CJC Open 6 (2024) 86–95

Systematic Review/Meta-analysis

A Systematic Review of Delayed High-Grade Atrioventricular Block After Transcatheter Aortic Valve Implantation

Karan Rao, MD, BMed, MPH,[a,b,c] Bernard Chan, MBBS,[a,c] Alexandra Baer, BSN, MSHM,[b] Peter Hansen, MBBS, PhD,[a,b] and Ravinay Bhindi, MBBS, PhD[a,b,c]

[a] *Department of Cardiology, Royal North Shore Hospital, Sydney, Australia*
[b] *Department of Cardiology, North Shore Private Hospital, Sydney, Australia*
[c] *University of Sydney, Sydney, Australia*

Published in:

CJC Open 2024 Vol. 6 Issue 2 Pages 86-95

Presented at:

Australia and New Zealand Endovascular Therapies (ANZET) Annual Scientific Meeting 2023

DOI: 10.1016/j.cjco.2023.10.003

Author contribution statement:

This chapter is published work for which I was first author. I conceived and designed the study, collected and analysed the data, interpreted the findings, and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

A systematic review of delayed high-grade atrioventricular block after transcatheter aortic valve implantation

Karan Rao MD, BMed, MPH [1, 2, 3], Bernard Chan MBBS[1, 3], Alexandra Baer BSN, MSHM[2], Peter Hansen MBBS, PhD[1, 2] & Ravinay Bhindi MBBS, PhD[1, 2, 3]

[1] Royal North Shore Hospital, Sydney, Australia

[2] North Shore Private Hospital, Sydney, Australia

[3] University of Sydney, Australia

Corresponding author:

Professor Ravinay Bhindi

Royal North Shore Hospital, Reserve Road, St. Leonards, 2065.

Email: ravinay.bhindi@sydney.edu.au

Short Title: Incidence of delayed HGAVB post TAVI

Word count: 4157 (excludes abstract and references)

Funding: This is an investigator initiated and funded project. No external funding was sought. Dr. Karan Rao is supported through a Heart Research Australia PhD Scholarship.

Disclosures: The authors have no disclosures or conflicts of interest to report.

The authors confirm that patient consent is not applicable to this article, as it is a systematic review of published literature.

3.1 Abstract

Background

High-grade atrioventricular (HGAVB) block is common after TAVI, often necessitating permanent pacemaker (PPM) implantation. *Delayed* HGAVB has varying definitions, but typically refers to onset 48 hours after TAVI, or following discharge, and may cause syncope and sudden cardiac death. This review estimates the incidence of delayed HGAVB and identifies limitations of current literature.

Methods

A systematic review was performed of the following online databases: Medline, Cochrane, Web of Science, and Scopus. Studies which labelled the outcome of "delayed" or "late" atrioventricular block after TAVI were included, patients with prior PPM or aortic valve surgery were excluded. Initial search yielded 775 studies, which after screening, was narrowed to 19 studies.

Results

19 studies with 14898 patients were included. Mean age was 81.7 years, whilst 46.3% were male. Mean STS score was 5.6%, and 31.3% of patients had known atrial fibrillation. The most common access site was transfemoral (84.8%), whilst balloon-expandable valves were used in 62.1%, self-expanding valves in 34.0%, and mechanically expanding valves in 3.9% of cases. The incidence of delayed HGAVB ranged from 1.7-14.6% with significant methodological heterogeneity noted amongst the included studies.

Conclusions

Delayed HGAVB is a common and potentially serious complication of TAVI, with similar risk factors to acute HGAVB. With a move towards an early discharge strategy post TAVI, further prospective study of delayed HGAVB is warranted to improve understanding of predisposing factors, incidence, timing, and implications.

Keywords*: atrioventricular block; delayed; late; TAVI; conduction; aortic stenosis*

3.2 Introduction

High-grade atrioventricular block (HGAVB), which comprises of third-degree or second-degree (Mobitz Type II) atrioventricular (AV) block, is not infrequent following transcatheter aortic valve implantation (TAVI), with a reported incidence between 9-26% and often necessitating permanent pacemaker (PPM) implantation (79, 91). The definition of *delayed* HGAVB varies in the literature, but generally refers to the onset of HGAVB 48 hours after TAVI, or following discharge, as per the most recent American College of Cardiology (ACC) consensus statement(92). The current ACC and European guidelines recommend (Class 1) permanent pacing in patients with persistent HGAVB at 24-48 hours post TAVI(92, 93).

The mechanism of HGAVB in TAVI is via mechanical compression of the bundle of His, left bundle branch or less commonly the AV node. The bundle of His emerges and bifurcates at the base of the membranous ventricular septum, which explains why the membranous septal length and implantation depth are both powerful predictors of HGAVB post-TAVI (47). Other predictors include pre-existing right bundle branch block (RBBB), self-expanding valves, significant oversizing, and a post-procedural increase in QRS or PR interval (94-96). Electrophysiology study (EPS) including HV interval measurement and induction of AV Wenckebach through incremental atrial pacing have a strong negative but poor positive predictive value for PPM after TAVI (68, 69).

Despite multiple known predictors, there is currently no sensitive nor specific method of identifying patients likely to develop HGAVB post-TAVI. Moreover, there is little understanding about the timing of delayed HGAVB; whilst predominantly occurring within the first week, HGAVB can also occur beyond 30 days (84, 97, 98). When unrecognised, HGAVB can lead to significant bradycardia, manifesting as pre-syncope, syncope or sudden

cardiac death. A substantial proportion of unexplained sudden cardiac death following TAVI may be secondary to unrecognised delayed HGAVB given both adverse outcomes share similar predictors (98, 99).

As improved procedural technique and peri-procedural care have reduced the length of post-TAVI hospital admissions, the incidence of delayed HGAVB necessitating PPM insertion following hospital discharge has increased (100, 101). This systematic review investigates the incidence of delayed HGAVB or new permanent pacemaker implantation in patients without a prior pacemaker or aortic valve surgery, and aims to identify the current limitations of the literature.

3.3 Methods

A systematic review searching the following electronic databases was performed: Medline, Scopus, Web of Science and Cochrane, from January 1, 2000, until May 15, 2022. Study screening was performed by two authors (KR/BC). Keywords searched were “TAVI”, “TAVR”, “transcatheter aortic valve implantation” or “transcatheter aortic valve replacement”; combined with “conduction disturbance”, “bradycardia”, “bradyarrhythmia” or “atrioventricular block”. Free word and MeSH term searches were conducted on “TAVI”, “TAVR”, “transcatheter (aorta*)” and “block” or “pacemaker” or “bradycardia” or “conduction” or arrhythmia” combined with “delay” or “late”. The review included all studies which measured the desired outcome of delayed HGAVB, had accessible results, and were published in English. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded. Review articles were omitted due to potential publication bias and result duplication.

Due to the varying definitions of delayed HGAVB, only studies which defined it as occurring at least 24 hours after the TAVI were included. There was no discrimination of total follow up periods or valve design, and both prospective and retrospective studies were included.

Patients with prior permanent pacemaker implantation or aortic valve surgery were removed from the total population by the authors prior to calculating the incidence of delayed HGAVB.

A standardised data collection template was used for data extraction, including baseline demographics, study design, exclusion criteria, definition of delayed HGAVB and method of diagnosis, length of follow up, valve types used, prevalence of pre-existing right bundle branch block, prevalence of pre-existing atrial fibrillation, and incidence of delayed HGAVB.

3.4 Results

The initial search strategy yielded 775 results, and after removal of duplicates 370 studies were removed. Through title and abstract screening, a further 378 were removed, and 27 studies remained for full study review. After application of the selection criteria, 8 further studies were excluded. The remaining 19 studies were further screened and a bias assessment was performed using the ROBINS-I tool(102) (Figure 1: PRISMA flow chart). Data extraction and critical appraisal was conducted by two reviewers (KR and BC), and results were reviewed by the senior investigators (PH and RB).

The 19 studies included in this review consisted of a total of 14898 patients. Of the included studies, 11 (58%) were retrospectively performed and 8 (42%) were prospectively performed. All studies were non-randomised and observational. Delayed HGAVB was measured using a continuous monitoring method (either ambulatory event monitoring or an implantable loop

recorder) in 7 (37%) of the studies, whilst the remainder used non-continuous monitoring to measure the outcome, either through ECG, clinical features, or clinician-initiated permanent pacemaker implantation.

Baseline Characteristics

Overall, the mean age was 81.7 years, whilst 46.3% of the patients were male and the mean STS score was 5.6% (Table 1). Almost a third (31.5%) of patients were found to have pre-existing atrial fibrillation. The most commonly deployed valve type was balloon-expanding (62.1%) followed by self-expanding (34.0%), and then mechanically expanding valves (3.9%). The most common approach was transfemoral (84.8%).

Definition and incidence of delayed HGAVB

The definition of delayed HGAVB varied in the literature. Sixteen studies defined delayed HGAVB as either post discharge, or between 24- and 72-hours following TAVI. The remainder defined delayed HGAVB as either after 7 days or after 30 days. Lengths of follow up were also variable between the studies, ranging from 14 days to 5 years. Due to the variation in follow up periods and influence on detection of the primary outcome, Tables 2-5 split the studies by total follow up period.

The incidence of *delayed* HGAVB *or* new delayed permanent pacemaker implantation, ranged from 1.7% to 14.6% across the included studies (Tables 2-5). Due to the high degree of heterogeneity, a pooled incidence was not calculated on all included studies. Instead, a sub-analysis was performed on 5 prospective studies (84, 103-106), which used a similar definition of delayed HGAVB (48 hours after TAVI or after discharge), had the lowest calculated risk of bias (low or low-moderate), and contained overall low heterogeneity (I^2 =

34%). The estimated overall incidence of these 5 studies was 5.17% (95% CI 3.29-7.04) (Table 6).

3.5 Discussion

In this systematic review of 19 studies with 14898 patients, the incidence of delayed HGAVB after TAVI ranged from 1.7-14.6%. There was significant variation amongst the study methodologies, which prohibited a meta-analysis and calculation of pooled incidence. However, a sub-analysis of 5 select studies, with a similar definition of delayed HGAVB, yielded an estimated incidence of 5.17%. The major points of difference between the studies were their inclusion criteria, definitions of delayed HGAVB, follow up periods and methods of measuring HGAVB. Overall, more rigorously measured prospective data is required to better estimate the true incidence of this phenomenon.

A persistent confounder in all studies investigating atrioventricular block after TAVI is pre-existing subclinical conduction disease. Due to the proximity of the AV node to the aortic valve, calcium deposits often extend into the conduction system in patients with degenerative aortic stenosis, resulting in subclinical conduction disease even prior to their TAVI. It has been shown that by monitoring patients in the 24 hours prior to their TAVI, subclinical bradyarrhythmia was found in up to 6% (107). Furthermore, the mean age of patients included in this review was 81.7 years, and advanced age, along with comorbidities such as diabetes, hypertension, and heart failure, are associated with left bundle-branch block and bradyarrhythmia, irrespective of TAVI (108-110).

The differing definitions of delayed HGAVB likely stems from the lack of a consensus definition. Studies were included based on the self-labelled outcome of “delayed” or “late”

HGAVB, however the defined time-period post-TAVI varied from as early as 2 hours post procedure, up to 30 days post procedure. Studies which defined delayed HGAVB as temporally later than others, such as Biancari (2021), Fischer (2018) and Lee (2021) may have missed a significant proportion of patients. In the absence of a universally accepted definition of delayed HGAVB, it is important to consider what the *correct* or appropriate cut-off may be.

From a patient safety perspective, the highest risk of adverse outcomes from HGAVB is following hospital discharge, and thus this is perhaps the most practical definition of *delayed* HGAVB. Whilst this was incorporated as a definition in 5 studies, it is difficult to standardise *time to discharge,* as practices vary based on patients, operators, and institutions. Perhaps this is why 48 hours following TAVI was the most commonly utilised definition (n=6). Considering most TAVI patients are able to be discharged in the first 48 hours(111), this may be the most appropriate definition. Creating a formalised definition can allow future studies, and larger national registries, to report this outcome homogenously.

The method used to detect delayed HGAVB also varied amongst the literature, which also likely impacted their results. The most accurate, or "gold-standard", measurement is via a continuous monitoring technique, such as an implantable loop recorder (ILR), or ambulatory electrocardiographic monitoring (AEM). However, this was only seen in 7 (33%) of the studies.

The remainder 14 studies utilised either periodic ECGs at designated time points, clinical symptoms, or treating physician mandated pacemaker implantation based on these two prior features. These cross-sectional methods may miss HGAVB episodes that occurred transiently

or remained subclinical, likely underestimating the true incidence. Similarly, post-TAVI pacemaker dependency has also been considered as a marker of persistent conduction disease; however, this measurement also appears flawed as it fails to consider paroxysmal AV block.

In studies which used a permanent pacemaker implantation as the defined time-point for delayed HGAVB, it must be considered that the threshold often varies across centres, which is an important limitation of this study. For example, in centres where permanent pacemakers may be implanted *early* due to high-risk features alone, there may be a potential underestimation of the incidence of delayed HGAVB.

Whilst the highest risk period for HGAVB is immediately following TAVI, the risk appears to steadily reduce over time, persisting up to 12-24 months. Tables 2-5 divide the studies by grouping their follow up periods. The four studies with "long" follow up periods of greater than a year (Table 5), were all performed retrospectively with non-continuous parameters to measure delayed HGAVB. Together, these studies made up 62% of the total participants included in the systematic review. By extending the follow up period, there is an increased risk of capturing conduction disease unrelated to the initial TAVI.

The use of self-expanding valves is a well-documented risk factor for acute HGAVB. Historically, larger profile valves, such as the self-expanding Evolute (Medtronic; Dublin, Ireland) or Portico (Abbott; Chicago, Illinois, United States) platforms, as well as the now discontinued, mechanically-expanding Lotus valve (Boston Scientific; Marlborough, Massachusetts, United States) have resulted in higher rates of conduction abnormalities, since they impart greater radial tension and require deeper implantation into the left ventricular

outflow tract (36, 37). A possible exception is the ACURATE Neo (Boston Scientific, Marlborough, Massachusetts, United States) self-expanding valve, which is engineered to impart more balanced symmetrical radial force, which may explain the comparatively lower pacemaker rates (112).

Different inclusion criteria between the studies are also an influential determinant of delayed HGAVB. Four of the studies *selectively* included patients with pre-existing bundle branch block, a well-documented risk factor for post-TAVI acute pacemaker implantation. Rodes-Cabau (2018), Tovie-Brodie (2017) and Fischer (2018) only included patients with a pre-existing or new-persistent LBBB post TAVI. LBBB is common post-TAVI, occurring in up to 40% of patients (113), and independently results in a threefold increased risk of PPM post TAVI (39).

Similarly, RBBB has a prevalence of 10-14% (99, 114, 115) in patients prior to TAVI, and correlates with up to a five-fold greater risk of pacemaker implantation (99, 115). Amongst the included studies, the prevalence of pre-existing RBBB ranged from 5.0%-17.9%, and thus this variability may also account for differing outcomes.

Clinical implications of delayed HGAVB

Approximately 9% of all *cardiac* death up to two years post TAVI is from *unexplained* sudden cardiac death, which has retrospectively been attributed to bradycardic arrest secondary to delayed HGAVB in the absence of other obvious causes (116). Whilst delayed HGAVB can be prevented and treated with timely pacemaker implantation, the threshold varies across centres, and whilst not in the scope of this review, remains a key decision after TAVI.

Whilst pacemaker implantation remains common after TAVI, it may cause cardiac dyssynchrony and progression of tricuspid regurgitation. There are conflicting results in two major studies evaluating the long-term outcomes of patients requiring a new pacemaker after TAVI(117, 118), however a recent meta-analysis suggested higher all-cause mortality and heart failure related re-hospitalisation(119). Regardless, with a paradigm shift towards TAVI in younger and low surgical risk patients, methods to prevent conduction disease are paramount. Additionally, conduction system pacing may result in a shorter QRS, better ventricular synchrony, and improved haemodynamic result compared to right ventricular pacing, and may help to improve the prognosis of post-TAVI conduction disease(120).

Therefore, the absence of *conduction abnormalities* has been key criteria in classifying patients as "low discharge risk" in two large North American studies(121, 122) which validated early discharge following TAVI. The presence of a pre-existing RBBB, a persistent new LBBB along with the use of self-expanding valves have generally been viewed as much higher risk for *early discharge* due to the risk of impending HGAVB. For this reason, perhaps such high-risk patients should be monitored in hospital for at least 48 hours post TAVI and clinicians may even consider longer term post-discharge ambulatory rhythm monitoring and earlier follow up. The current European Society of Cardiology (ESC) pacing guidelines recommend (Class IIA) permanent pacing in patients with pre-existing RBBB with any new conduction disease noted post TAVI. Similarly, it is recommended that in patients with a new LBBB over 150ms, or a PR interval over 240ms, the use of continuous rhythm monitoring, or the measurement of a His-Ventricular (HV) interval over 70 milliseconds (ms), can aid in decision making(93).

Due to the difficulty in predicting delayed HGAVB, various studies have evaluated the use of electrophysiology studies (EPS) to further risk stratify patients. It may serve a role in *intermediate* risk patients, such as those with a new persistent LBBB or RBBB, or PR prolongation over 40 ms after TAVI. One group demonstrated that an absolute increase in HV interval pre and post TAVI, or an absolute HV interval >65ms post TAVI may predict subsequent AV block(68). The use of the HV interval post TAVI to predict delayed HGAVB has been subsequently validated by future studies that have used cut-offs between 55-70ms(123, 124). Rapid atrial pacing provoked second degree AV block (AV Wenckebach cycle length) may also have utility, with Krishnaswamy et al. demonstrating that patients who did not develop pacing induced AV Wenckebach up to 120 beats per minute had an extremely low likelihood of requiring permanent pacemaker implantation(69). Other risk factors for acute high-grade AV block include the use of deeply implanted valves, along with patient factors such as aortic valve calcification and short membranous septum length(125).

A currently actively recruiting Australian study, CONDUCT-TAVI (ACTRN12621001700820), is aiming to provide further clarity on clinical predictors of delayed HGAVB by studying conduction disturbances in transfemoral TAVI patients with an implantable loop recorder for two years. This study will prospectively analyse the frequency and timing of delayed HGAVB post TAVI, as well as evaluate 12 lead ECG, computed tomography and electrophysiology study-based risk factors.

3.6 Conclusions

Despite the heterogeneity within currently published literature, it is evident that delayed HGAVB is not infrequent after TAVI, with important clinical ramifications. With newer generation valves, greater experience, and higher implant depths, pacemaker rates are steadily reducing.

Predicting *delayed* HGAVB remains difficult, and further study into novel methods such as utilising targeted pre and post TAVI electrophysiology studies, measuring the membranous septum length and quantifying cusp calcification may assist us moving forward. In the future, a consensus definition of delayed HGAVB, along with well powered prospective studies which incorporate continuous rhythm monitoring for extended periods are most likely to advance our understanding.

3.7 Tables and Figures

Table 1: Summary demographics (n=19)

Summary baseline characteristics	**Results**
Total patients	14898
Age, mean (SD)	81.7 (+/- 4.7)
Gender *Male %*	 46.3
STS score, mean%	5.6 *total n=11498
Pre-existing atrial fibrillation, n (%)	4654 (31.3) *total n=14103
Pre-existing right bundle branch block (RBBB), n (%)	1144 (8.6) *total n=13001
Valve type *Balloon-expandable, n (%)* *Self-expandable, n (%)* *Mechanically-expandable, n (%)*	 9707 (62.1) 5305 (34.0) 608 (3.9)
Transfemoral access site, n (%)	10395 (84.8) *total n=12265

Table 2: Studies with follow up period up 7-14 days

#	Author (Year)	Country	Study type	Exclusion criteria	Special Inclusion criteria	Delayed HGAVB definition	Measuring HGAVB	Maximum follow up period	Total patients	Age (mean, years)	Male %	STS %	Pre-existing AF%	Pre-existing RBBB%	Valve used	% Transfemoral	%incidence HGAVB	Bias (ROBINS-I tool)
1	De-Torres Alba (2018)(126)	Germany	Retro	Prior PPM, ViV	n/a	≥48 hours	AEM	7 days	606	81.6	44.4	n/a	n/a	6.1	BE (100%)	94.4%	2.8%	Moderate
2	Muntane-Carol (2021) (103)	Canada, Spain	Prosp	Prior PPM, ViV	n/a	After discharge	AEM	14 days	459	79.0	54.7	3.6	27.5	9.4	BE (85.6%), SE (14.2%), ME (0.2%)	88.7%	4.6%	Low

Table 3: Studies with follow up period up 30-90 days

#	Author (Year)	Country	Study type	Exclusion criteria	Special Inclusion criteria	Delayed HGAVB definition	Measuring HGAVB	Maximum follow up period	Total patients	Age (mean, years)	Male %	STS %	Pre-existing AF%	Pre-existing RBBB%	Valve used	% Transfemoral	%incidence HGAVB	Bias (ROBINS-I tool)
3	El-Sabawi (2021)(127)	USA	Retro	Prior PPM, ViV	n/a	≥24 hours	Daily ECG until discharge, then periodic ECG guided by clinical features	30 days	953	81.1	56.1	7.1	37.5	12.5	BE (85.4%), SE (14.6%)	82.2%	3.5%	Moderate
4	Kagase (2021)(128)	Japan	Retro	Prior PPM, ViV	n/a	≥24 hours and Complete (3rd degree) AV block only	Periodic ECG	30 days	696	85.4	33.5	7.9	19.7	12.7	BE (100%)	n/a	2.3%	Serious
5	Ream (2019)(84)	USA	Prosp	Prior PPM, ViV	n/a	≥48 hours	AEM	30 days	148	78.0	54.1	n/a	29.7	17.3	BE (75.7%), SE (24.3%)	n/a	8.1%	Low-Moderate
6	Tarakji (2022)(105)	USA	Prosp	Prior PPM, ViV	n/a	PPM insertion after discharge	AEM	90 days	96	80.3	71.9	n/a	17.7	17.9	BE (94.8%), SE (5.2%)	n/a	3.1%	Low-Moderate
7	Tian (2019)(104)	USA	Prosp	Prior PPM, ViV	n/a	After discharge	AEM	30 days	197	81.0	61.9	6.4	37.6	17.3	BE (93.4%), SE (6.6%)	n/a	4.6%	Low-Moderate
8	Toggweiler (2016)(129)	Switzerland	Prosp	Prior PPM, ViV	n/a	After 1st post procedure ECG	AEM 72 hours, periodic ECG thereafter	30 days	1064	82.0	47.7	6.2	22.0	5.0	BE (52.3%), SE (47.7%)	92.2%	6.7%	Moderate

Table 4: Studies with follow up period of 1 year

#	Author (Year)	Country	Study type	Exclusion criteria	Special Inclusion criteria	Delayed HGAVB definition	Measuring HGAVB	Maximum follow up period	Total patients	Age (mean, years)	Male %	STS %	Pre-existing AF%	Pre-existing RBBB%	Valve used	% Transfemoral	%incidence HGAVB	Bias (ROBINS-I tool)
9	Chorianopoulous (2012)(130)	Germany	Retro	Prior PPM, ViV	n/a	≥48 hours	Periodic ECG, clinical decision for PPM	1 year	130	81.3	41.5	n/a	n/a	13.8	SE (100%)	100.0%	7.7%	Moderate
10	Khan (2022)(131)	USA	Retro	Prior PPM, ViV	n/a	≥7 days	Clinical decision for PPM	1 year	285	83.9	47.4	n/a	23.5	7.5	BE (79.6%), SE (20.4%)	89.5%	7.4%	Moderate
11	Lee (2021)(132)	Japan	Retro	Prior PPM, ViV	n/a	≥1 month	AEM until discharge, periodic ECG thereafter	1 year	246	85.0	34.6	6.4	22.0	14.0	BE (23.2%), SE (70.3%)	n/a	4.1%	Moderate
12	Mangieri (2018)(98)	Italy	Retro	Prior PPM, ViV, acute HGAVB <48 hours	n/a	≥48 hours	Periodic ECG and clinical decision for PPM	1 year	611	84.4	43.7	6.9	31.6	6.1	BE (51.7%), SE (42.1%), ME (4.6%)	100.0%	8.8%	Moderate
13	Reiter (2021)(106)	Austria	Prosp	Prior PPM, ViV, permanent AF, acute HGAVB <48 hours	n/a	≥48 hours and complete (3rd degree) AV block only	ILR	1 year	59	80.3	39.0	n/a	n/a	6.8	SE (100%)	100.0%	11.9%	Low-Moderate
14	Rodes-Cabau (2018)(133)	Spain	Prosp	Prior PPM, ViV	Persistent LBBB post TAVI day 3	≥72 hrs	ILR	1 year	103	80.0	42.7	5.0	26.2	0	BE (48.5%), SE (51.5%)	86.4%	14.6%	Serious
15	Tovia-Brodie (2017)(124)	Israel	Prosp	Prior PPM, ViV	Persistent LBBB post TAVI day 2	PPM insertion after discharge	Clinical decision for PPM	1 year	81	82.0	42.0	3.3	11.1	0	BE (32.1%), SE (67.9%)	n/a	3.7%	Serious

Table 5: Studies with variable and longer follow up periods of over 1 year

#	Author (Year)	Country	Study type	Exclusion criteria	Special Inclusion criteria	Delayed HGAVB definition	Measuring HGAVB	Maximum follow up period	Total patients	Age (mean, years)	Male %	STS %	Pre-existing AF%	Pre-existing RBBB%	Valve used	% Transfemoral	%incidence HGAVB	Bias (ROBINS-I tool)
16	Biancari (2021)(97)	Finland	Retro	Prior PPM, ViV	n/a	PPM insertion ≥ 30 days	Clinical decision for PPM	5 years	1897	81.2	44.2	4.5	40.9	n/a	BE (68.5%), SE (20.7%),	n/a	6.2%	Moderate

															ME (10.8%)			
17	Elchinova (2021)(134)	Switzerland	Retro	Prior PPM, ViV, all patients with acute HGAVB	n/a	PPM insertion after discharge	Periodic ECG and clinical decision for PPM	Variable, median 1095 days	1059	81.7	47.2	5.4	33.9	6.3	BE (52.3%), SE (40.8%), ME (6.7%)	89.1%	4.3%	Moderate
18	Fischer (2018)(135)	Canada	Retro	Prior PPM, ViV	LBBB on baseline ECG	PPM insertion ≥ 30 days	Periodic ECG and clinical decision for PPM	Variable, median 22 months	3404	81.0	47.3	5.5	27.8	0	BE (53.9%), SE (45.8%)	81.2%	1.7%	Serious
19	Kooistra (2020)(136)	Netherlands	Retro	Prior PPM, ViV	n/a	PPM insertion ≥48 hours	Telemetry (48 hours), periodic ECG guided by clinical decision to implant PPM	5 years	2804	82.0	44.5	n/a	34.6	11.0	BE (55.8%), SE (36.7%), ME (7.2%)	75.7%	2.2%	Moderate

Table 6: Sub-analysis of selected prospective studies with continuous monitoring methods and lowest assessment of bias

Author	Study type	Delayed HGAVB definition	Method of measuring HGAVB	Follow Up	Patients	Valve type	Total delayed HGAVB events	% incidence of delayed HGAVB	Bias (ROBINS-I tool)
Muntane-Carol (2021)(103)	Prospective	After discharge	AEM	14 days	459	BE (85.6%), SE (14.2%), ME (0.2%)	21	4.6%	Low
Ream (2019)(84)	Prospective	≥48 hours	AEM	30 days	148	BE (75.7%), SE (24.3%)	12	8.1%	Low-Moderate
Reiter (2021)(106)	Prospective	≥48 hours and complete (3rd degree) AV block only	ILR	1 year	59	SE (100%)	7	11.9%	Low-Moderate
Tarakji (2022)(105)	Prospective	PPM insertion after discharge	AEM	3 months	96	BE (94.8%), SE (5.2%)	3	3.1%	Low-Moderate
Tian (2019)(104)	Prospective	After discharge	AEM	30 days	197	BE (93.4%), SE (6.6%)	9	4.6%	Low-Moderate
n = 959, Incidence (%) of delayed HGAVB (IV, Random, 95%CI) = 5.17 (3.29-7.04) | Heterogeneity: I^2 = 34%									

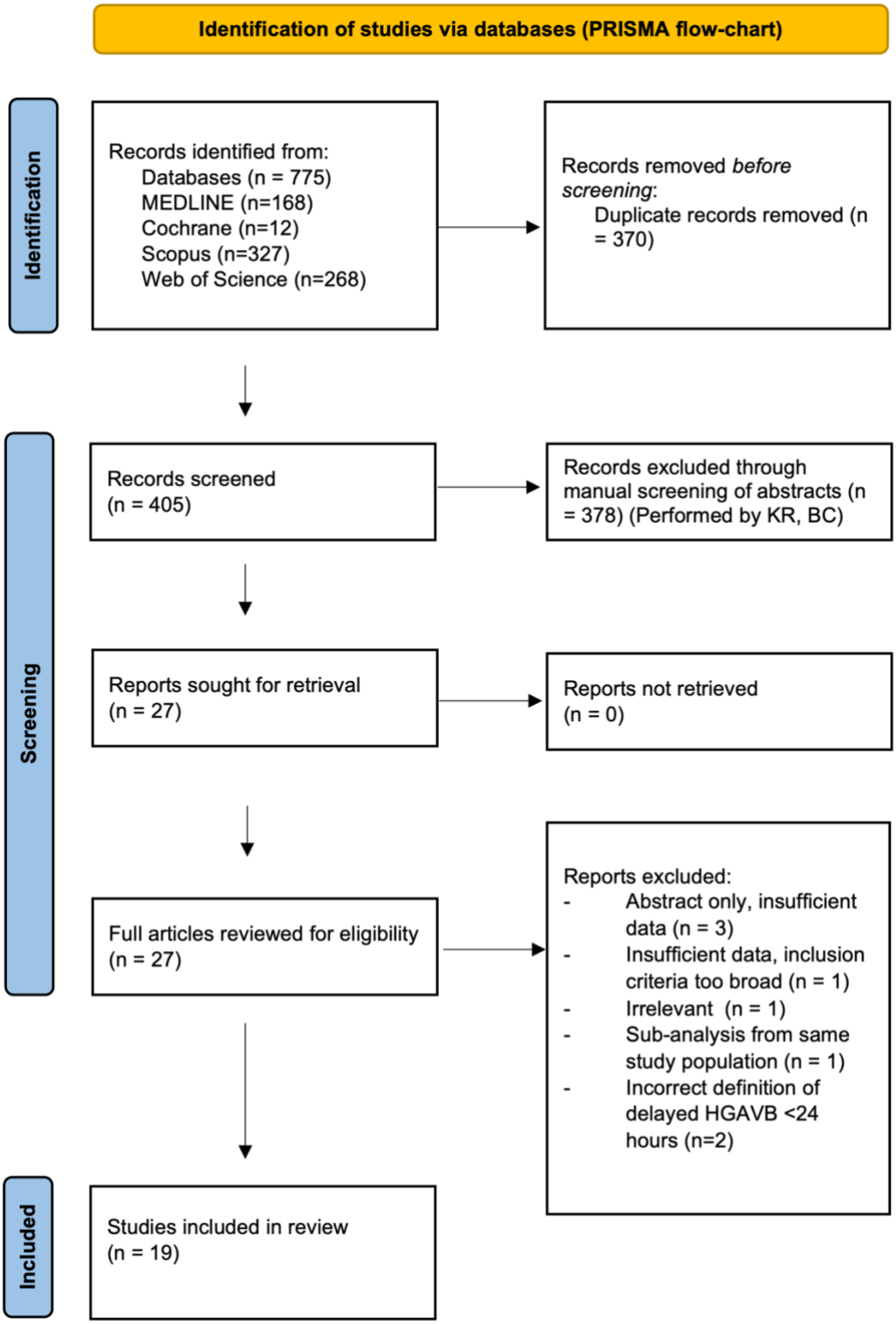

Figure 1: PRISMA Flowchart for identification, screening, and inclusion of studies

CHAPTER 4: The prognostic impact of a new bundle branch block after TAVI, a systematic review and meta-analysis

Structural Heart 9 (2025) 100392

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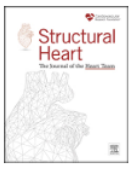


Original Research

The Prognostic Relevance of a New Bundle Branch Block After Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-Analysis

Karan Rao, MD, BMed, MPH [a,b,c], Mohammed Ahmed, BEng (Mech) [c], Daniel Brieger, MBBS [a], Alexandra Baer, BSN, MSHM [b], Peter Hansen, MBBS, PhD [a,b], Ravinay Bhindi, MBBS, PhD [a,b,c,*]

[a] Royal North Shore Hospital, Sydney, Australia
[b] North Shore Private Hospital, Sydney, Australia
[c] University of Sydney, Australia

Published in:

Structural Heart Issue 9 (2025)

Presented at:

PCR London Valves Conference 2024

Author contribution statement:

This chapter is published work for which I was first author. I conceived and designed the study, collected and analysed the data, interpreted the findings, and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

The prognostic relevance of a new bundle branch block after transcatheter aortic valve implantation: A systematic review and meta-analysis

Karan Rao MD, BMed, MPH[1, 2, 3], Mohammed Ahmed BEng (Mech)[3], Daniel Brieger MBBS[1], Alexandra Baer BSN, MSHM[2], Peter Hansen MBBS, PhD[1, 2] & Ravinay Bhindi MBBS, PhD[1, 2, 3]

[1] Royal North Shore Hospital, Sydney, Australia

[2] North Shore Private Hospital, Sydney, Australia

[3] University of Sydney, Australia

Corresponding author:

Professor Ravinay Bhindi

Royal North Shore Hospital, Reserve Road, St. Leonards, 2065.

Email: ravinay.bhindi@sydney.edu.au

Short Title: The prognostic relevance of new bundle branch block after TAVI

Word count: 4426 (all inclusive)

Funding: This is an investigator initiated and funded project. No external funding was sought. Dr. Karan Rao is supported through a National Health and Medical Research Council (NHMRC) and Heart Research Australia Postgraduate Scholarship.

Disclosures: The authors have no disclosures or conflicts of interest to report.

The authors confirm that patient consent is not applicable to this article, as it is a systematic review and meta-analysis of published literature.

4.1 Abstract

Background

Interference with the cardiac conduction system is common after transcatheter aortic valve implantation (TAVI), manifesting as atrioventricular block, or more commonly, new-onset persistent left bundle branch block (NOP-LBBB). Bundle branch block results in ventricular dyssynchrony and reduced cardiac output and may be associated with a poorer prognosis. This systematic review and meta-analysis evaluates the prognostic impact of a left or right bundle branch block after TAVI.

Methods

A systematic review was performed of the following online databases: PubMed, Medline, Scopus and Web of Science, including English language studies from 2014-2024. Two separate searches for conducted for NOP-LBBB and new-onset RBBB (NOP-RBBB). The New York Ottawa Scale (NOS) was used to evaluate risk of bias.

Results

23 studies totalling 18875 patients were included for NOP-LBBB, whilst 5 studies with a total of 3525 patients were included for NOP-RBBB. NOP-LBBB was associated with higher all-cause mortality at 1-year [RR 1.41 (95% CI 1.12-1.78), I^2=49%, p<0.01], cardiovascular mortality [RR 1.34 (95% CI 1.02-1.75), I^2=60%, p=0.02], heart failure related rehospitalisation [RR 1.56 (95% CI 1.31-1.84), I^2=47%, p<0.01], and permanent pacemaker implantation at 1 year [RR 3.05 (95% CI 2.39-3.89),I^2=14%, p<0.01]. NOP-RBBB was not associated with higher all-cause mortality at 1 year [RR 1.74 (95% CI 0.88-3.46), I^2=93%, p=0.11], however increased the risk of pacemaker implantation at 1-year [RR 4.68 (95% CI 3.60-6.08), I^2=67%, p<0.01].

Conclusion

NOP-LBBB is associated with higher mortality and heart-failure rehospitalisation after TAVI, whilst both NOP-LBBB and NOP-RBBB increase the risk of permanent pacemaker implantation at 1 year after TAVI.

4.2 Introduction

Transcatheter aortic valve implantation (TAVI) is a highly effective and minimally invasive treatment option for severe aortic stenosis and can be offered to patients of all surgical risk(137, 138). As of 2019, it has surpassed surgical aortic valve replacement (SAVR) as the primary treatment modality for AS(139).

Interference with the conduction system is not an infrequent complication of TAVI. This occurs primarily due to the anatomical proximity of the atrioventricular node, bundle of His, and left bundle branch to the aortic annulus and left ventricular outflow tract, which may be disrupted by the insertion of a transcatheter heart valve. A new permanent pacemaker is required in 11.3%(140) of cases, whilst the most common conduction abnormality is a new-onset persistent left bundle branch block (NOP-LBBB) which is seen in 16.3%(141). New-onset persistent RBBB (NOP-RBBB) is a much rarer occurrence and is thus not as well studied or described in the literature.

New bundle branch block is no longer considered a benign outcome of TAVI, as the resulting ventricular dyssynchrony may manifest as reduced cardiac output resulting in increased mortality and heart failure, as well as increasing the risk of complete atrioventricular block(142-145). The aim of this systematic review and meta-analysis is to evaluate the mid to

long term prognostic impact of a left or right bundle branch block after TAVI, with respect to mortality, heart failure-related re-hospitalisation and new permanent pacemaker implantation.

4.3 Methods

A systematic review searching the following electronic databases was performed: PubMed, Medline, Scopus and Web of Science from January 1, 2014, until April 1, 2024. Study screening was performed by three authors (KR, MA and DB).

For the LBBB arm of the search, the keywords searched were “TAVI”, “TAVR”, “transcatheter aortic valve implantation” or “transcatheter aortic valve replacement”; combined with “left bundle branch block” or “LBBB”. Free word and MeSH term searches were conducted on “TAVI”, “TAVR”, “transcatheter (aorta*)” and “left bundle branch block” or “LBBB”. The RBBB study screening was performed with similar search terms, with replacement of LBBB with RBBB.

The review included all studies or abstracts which had accessible results and were published in English. Case reports, conference presentations, editorials and expert opinions were excluded. Review articles were omitted due to potential publication bias and result duplication. A standardised data collection template was used for data extraction, including baseline demographics, study design, inclusion or exclusion criteria, incidence, and definition of persistent new LBBB or RBBB, length of follow up and valve type used.

Patients were divided into two groups, with and without new persistent bundle branch block. The primary outcome was all-cause mortality at 1 year, whilst secondary outcomes included all-cause mid-term (1-5 years) mortality, cardiovascular mortality, heart failure

rehospitalisation and new permanent pacemaker at 1 year. This review has been registered on PROSPERO (CRD42024533524).

Statistical Analysis

Meta-analysis was conducted using Review Manager (RevMan) Version 5.4. The Mantel-Haenszel statistical method was used with a random effects model to compute a risk ratio (RR) with a 95% confidence interval (CI). The I^2 test for heterogeneity was used. $I^2 < 30\%$ was considered low heterogeneity, I^2 30-60% considered moderate and $I^2 > 60\%$ was considered high or considerable heterogeneity. All *p*-values were two-tailed, and $p<0.05$ was considered statistically significant.

4.4 Results

New-onset persistent LBBB

The initial search strategy yielded 1250 results, and after removal of duplicates 577 studies were removed. Through title and abstract screening, a further 634 were removed, and 39 studies remained for full study review. After application of the selection criteria, 16 further studies were excluded. The remaining 23 studies were further screened, and a bias assessment was performed using the Newcastle Ottawa Scale (NOS) (Figure 1: PRISMA flow chart). Data extraction and critical appraisal was conducted by three reviewers (KR, MA & DB), and the results were reviewed with senior investigators (PH & RB). The 23 studies included in this review consisted of a total of 18875 patients. Of the included studies, 18 were performed retrospectively, whilst 5 were prospective. The NOS was used for bias adjudication, and all studies were determined to be of good or high quality (score 6-9).

Baseline characteristics

Table 1 summarises the key characteristics of the included LBBB-related studies which had similar demographics in terms of age, gender and surgical risk score. The most common access site was trans-femoral, and 15 studies used a combination of valves, whilst 6 used BEV exclusively, and 2 used SEV exclusively. The incidence of new persistent LBBB varied amongst the studies (9.6-47.5%) with an overall mean of 29.7%. The most common definition of NOP-LBBB was on ECG at hospital discharge (n=14), followed by at 1-month (n=4) and post-procedure/24 hours (n=4). Figure 2 reports the incidence of NOP-LBBB by year in all studies which defined NOP-LBBB as occurring at hospital discharge (n=14) and is arranged chronologically as well as by predominant valve type used.

The primary outcome of this meta-analysis was all-cause mortality at 1 year, which was reported in 13 out of 23 studies, and was found to be greater in patients with a NOP-LBBB; overall risk ratio [RR]: 1.41 (95% CI 1.12-1.78) with moderate heterogeneity: $I^2 = 49\%$, p=0<0.01 (Figure 3).

The secondary outcomes of this meta-analysis were mid-term all-cause mortality, cardiovascular mortality, heart-failure related hospitalisation and new permanent pacemaker at 1 year. The results are summarised in Figure 4.

When analysing mid-term all-cause mortality data was combined for all studies which reported mortality outcomes between 1-5 years (n=13). There was no increase in risk of all-cause mortality with a NOP-LBBB, with an overall RR of 1.09 (95% CI 0.99-1.21) with moderate heterogeneity: $I^2 = 49\%$, p = 0.02. Cardiovascular mortality was reported by 7 studies. The results favoured an increase in CV mortality at 1 year in the NOP-LBBB group; overall RR 1.34 (95% CI 1.02-1.75) with moderate to high heterogeneity: $I^2 = 60\%$, p = 0.02.

Heart failure rehospitalisation was reported by 14 studies, with a higher risk in patients with a NOP-LBBB; overall RR 1.56 (95% CI 1.31-1.84) with moderate heterogeneity: $I^2 = 47\%$, $p < 0.01$. New permanent pacemaker at 1 year was reported in 10 studies and was greater in patients with NOP-LBBB; RR 3.05 (95% CI 2.39-3.89) with low heterogeneity: $I^2 = 14\%$, $p < 0.01$.

New-onset persistent RBBB

The initial search strategy yielded 229 results, and after removal of duplicates 119 studies were removed. Through title and abstract screening, a further 97 were removed, and 13 underwent full review. After full text review and application of the selection criteria, 8 further studies were excluded. The remaining 5 underwent bias assessment using the NOS (Figure 1: PRISMA flow chart) and were included.

The 5 studies included consisted of a total of 3525 patients. Of the included studies, all were retrospective and of good or high quality (score 6-9) using the NOS. They key characteristics are displayed in Table 2. The incidence of NOP-RBBB varied amongst the studies varied (0.8-9.6%), and all studies defined NOP-RBBB as per the ECG prior to discharge.

The primary outcome of all-cause mortality was only reported in 2 studies (Figure 5), and there was no association of NOP-RBBB with all-cause mortality at 1-year, overall RR 1.74 (95% CI 0.88-3.46) and high heterogeneity: $I^2 = 93\%$, $p = 0.11$. The secondary outcome of new permanent pacemaker implantation at 1 year was reported by 5 studies, and NOP-RBBB was significantly associated with an increase in pacemaker implantation at 1 year: overall RR 4.68 (95% CI 3.60-6.08) with high heterogeneity: $I^2 = 67\%$, $p < 0.01$ (Figure 5). Other

secondary outcomes were not reported in the available studies and were therefore not included in the meta-analysis.

4.5 Discussion

This systematic review and meta-analysis offers the most up-to-date and comprehensive evaluation of the prognostic implications of a NOP-LBBB or NOP-RBBB after TAVI. The key results can be summarised as follows: (1) NOP-LBBB after TAVI is associated with a greater risk of all-cause mortality at 1 year compared to patients without NOP-LBBB; (2) NOP-LBBB after TAVI is associated with a greater risk of cardiovascular mortality and heart failure related rehospitalisation at mid to long-term follow up; (3) Both NOP-LBBB and NOP-RBBB after TAVI are associated with a greater risk of permanent pacemaker implantation at 1 year.

Our study found the incidence of NOP-LBBB after TAVI to be significantly higher than NOP-RBBB. This is explained by the anatomical proximity of the native conduction pathway to the aortic valve. The bundle of His is thought to emerge and bifurcate at the inferior margin of the membranous septum, exposing the left bundle branch and leaving it susceptible to interference from the inflow of an implanted THV. This mechanism also helps to explain the higher observed incidence of NOP-LBBB with taller framed self-expanding valves(146), which have may impart a greater radial force on the membranous septum. Whilst this study did not stratify the analysis on valve type, Figure 2 illustrates that the study with the highest incidence of NOP-LBBB (%) included *only* SEV patients, whereas the two studies with the lowest incidence of NOP-LBBB (%) included *only* BEV patients.

Of further interest is that Figure 2 illustrates that the incidence of NOP-LBBB is not only variable across studies, but also that it has not fallen with modern implant techniques and valve designs. This contrasts to the falling incidence of permanent pacemaker implantation, even in self-expanding valves, owing mostly to higher implantation depth using the cusp overlap technique(62). The cusp overlap technique facilitates higher implantation of the self-expanding valve by elongating the LVOT and isolating the non-coronary cusp. However, a meta-analysis published in 2023 by Sa et al.(147), did not show any difference in NOP-LBBB when the cusp-overlap technique was compared to standard coplanar implantation, which appears consistent with our findings.

The development of NOP-RBBB is more uncommon and cannot be explained as intuitively as the fibres are located on the right ventricular aspect of the ventricular septum. However, His-Bundle fibres are believed to be predestined for the left and right bundle(148), and thus one proposed theory(149) is that a THV may interrupt the right bundle much more *proximally* via direct or indirect means (calcium translocation). Another proposed aetiology is via septal ischaemia from embolic debris during THV deployment, although this requires validation(149).

On analysis of our primary outcome, we found NOP-LBBB increased the risk of all-cause mortality at 1 year, compared to those without a LBBB (RR 1.41, 95% CI 1.12-1.78), with moderate heterogeneity ($I^2 = 49\%$). One outlier in our results was Eschalier *et al.* (2019)(150) where the RR of all-cause mortality after NOP-LBBB was 0.25 (95% CI 0.03-2.14). This discrepant result is potentially explained by the study's small sample size (n=80), and its design, as it was conducted as a sub-analysis of a concurrently running separate prospective

study which was powered to investigate for changes in left ventricular function, rather than mortality at 1 year.

We also noted an increase in cardiovascular mortality and heart-failure related rehospitalizations in patients with NOP-LBBB. The adverse prognostic outcome of NOP-LBBB may at least partly explained by electrical and mechanical dyssynchrony, causing decreased cardiac output, higher residual LV volumes and negative cardiac remodelling(151). To date, there have been three prior meta-analyses assessing the prognostic impact of NOP-LBBB after TAVI. The first, published by Regueiro et al.(67) in 2016, found that NOP-LBBB increased cardiovascular death and PPM at 1 year and trended towards worse all-cause mortality at 1 year without reaching statistical significance. In 2020, Faroux et al.(152) published that NOP-LBBB increased risk of all-cause and cardiovascular mortality, as well as heart failure rehospitalisation and PPM at 1 year. These results were further substantiated most recently by Wang et al. (2022)(41), and are also similar to our results(153) which also include an additional five studies which were published after Wang et al. (2022)'s work.

Our study did not find a correlation between NOP-LBBB and mid-term all-cause mortality, which included follow up from 1-5 years. Whilst this may partly be attributed to varying follow up periods, a physiological explanation may be from conduction system recovery. Whilst immediate LBBB after TAVI is very common, occurring in in up to 40% of patients due to transient localised inflammation, up to a third of patients recover their conduction by hospital discharge, and close to two-thirds recover in 12 months(154). Thus, when studying the longer-term impacts of THV-induced LBBB, a "persistent" LBBB should perhaps be defined as manifesting past 12 months.

Our study is the first to meta-analyse the currently available prognostic data on NOP-RBBB after TAVI. Whilst we did not find an association between NOP-RBBB and all-cause mortality at 1 year, it must be noted that only 2 studies were available for analysis, both of which were retrospective with significant heterogeneity.

The evaluation of NOP-RBBB and the risk of pacemaker at 1 year was a more robust and clinically relevant analysis, with 5 available retrospective studies. We found that NOP-RBBB increased the risk of PPM 5-fold (RR 4.68) at 1 year, even more so than with NOP-LBBB (RR 3.08). Whilst there was still notable heterogeneity in the data (I^2=67%), the strength of this association may warrant further prospective research.

Regardless, implanters who note the development of a new bundle branch block may rightfully opt for longer ambulatory or invasive (implantable loop recorder) rhythm monitoring, although there is limited data available to recommend the duration of monitoring that would be sufficient. The role of a prophylactic pacemaker in patients with a new bundle branch block is also controversial, although a recently published French study demonstrated that in patients with a NOP-LBBB after TAVI, a His-Ventricle (HV) interval >70 milliseconds(40) conferred a greater risk of progression of complete heart block, and in such patients a preventative pacemaker may be justified.

Limitations

As a meta-analysis of observational studies, limited to the English language, we may have unintentionally introduced elements of bias. Our analysis of NOP-RBBB had high levels of heterogeneity, as did our analysis of NOP-LBBB and cardiovascular mortality, which influences the overall interpretation of these results. The likely drivers include varying

definitions of “persistent” bundle branch blocks, valve types used and cohort surgical risk scores. Furthermore, the duration of the QRS interval in both NOP-LBBB and NOP-RBBB populations may influence the likelihood of future high-grade atrioventricular conduction disease but was not available for analysis in the included studies. Finally, it should be noted that our search strategy and filtration of studies was based on our primary outcome, and secondary outcomes were reported from these included studies and were not specifically searched.

4.6 Conclusions

Patients with a NOP-LBBB after TAVI have greater risk of all-cause mortality at 1 year, as well as greater cardiovascular mortality, heart-failure hospitalisations and permanent pacemaker implantation. Whilst NOP-RBBB after TAVI is not as well studied, the results suggest a significantly increased risk of new pacemaker implantation at 1 year. Recognising the prognostic impact of bundle branch block after TAVI can help to guide implanters in pre-procedural planning, as well as post-procedural follow up care.

4.7 Tables and Figures

Author (year)	Country	Total Patients	Age (years) (LBBB/no LBBB)	Male% (LBBB/no LBBB)	New persistent LBBB Definition	Incidence p-LBBB (%)	Follow-up	Valve type	Surgical risk % (LBBB/no LBBB)	Femoral access%	Study Type	NOS Bias Score
Akdemir (2020)	USA	151	79 / 80	46 / 53	Hospital discharge	31.1	1 year	BEV, SEV	n/a	100%	Retrospective, single centre	7
Ashraf (2020)	USA	243	81 / 80	46 / 58	Post procedure	19.8	1 year	BEV	n/a	83%	Retrospective, single centre	7
Carraba (2015)	USA	92	81/81	53/52	Hospital discharge	37.0	1 year	SEV	Log. EuroScore 20.0 (cohort)	97%	Retrospective, single centre	7
Chamandi (2019)	Canada	1020	80/81	57/58	Hospital discharge	20.8	3 years (median)	BEV, SEV	STS 6.8/6.5	84%	Retrospective, multi-centre	8
Eschalier (2019)	France	80	82/82	53/63	24 hours	9.6	1 year	BEV, SEV	EuroScore II 3.5 (cohort)	76%	Prospective, single centre	6
Hamandi (2020)	USA	424	82/81	42/53	Post-procedure	12.3	1 year	BEV, SEV	STS 7.6/7.2	85%	Retrospective, single centre	7
Hein-Rothweiler (2017)	Germany	225	81/80	33/44	Hospital discharge	23.1	1 year	BEV	Log. EuroScore 16.9 / 17.3	100%	Retrospective, single centre	7
Houthuizen (2014)	Netherlands	412	80/81	57/41	12 months	26.9	3 years (median)	BEV, SEV	Log. EuroScore	63%	Retrospective, multi-centre	8

									16.4 (cohort)			
Jorgensen (2019)	Denmark	684	81/81	50/51	Hospital discharge	36.1	1 year	BEV, SEV	STS 3.1/3.3	93%	Prospective, single centre	9
Kessler (2019)	Germany	528	81/80	46/46	Post procedure	47.5	2 years	BEV, SEV, MEV	STS 6.6/6.7	n/a	Retrospective, single centre	8
Kim (2022)	South Korea	364	80/81	42/46	Hospital discharge or 7 days	11.3	1 year	BEV, SEV	STS 6.1/5.8	n/a	Retrospective, single centre	8
Lopez-Aguilera (2016)	Spain	153	78/77	45/59	Hospital discharge	36.0	5 years	SEV	STS 9.5/12.0	n/a	Prospective, single centre	9
Nazif (2019)	USA	1179	81/82	53/54	Hospital discharge	15.2	1 year	BEV	STS 5.5/5.5	83%	Prospective, multi-centre	9
Nazif (2014)	USA	1051	84/84	43/44	Hospital discharge	11.5	1 year	BEV	STS 11.3/11.1	57%	Prospective, multi-centre	9
Paracuellos (2021)	Spain	254	80/82	n/a	Hospital discharge	21.6	21 months (median)	BEV, SEV	EuroScore II 6.1 (cohort)	n/a	Retrospective, single centre (conference abstract)	6
Saito (2024)	Japan	5716	85/84	23/33	Hospital discharge	29.0	2 years	BEV, SEV	STS 6.0/6.1	90%	Retrospective, multicentre	8
Sammour (2023)	USA	612	80/81	66/52	1 month	11.4	3 years	BEV	STS 5.7 (cohort)	100%	Retrospective, single centre	9

Sasaki (2020)	Japan	231	84/84	24/37	1 month	12.6	431 days (median)	BEV, SEV	STS 5.3/6.2	n/a	Retrospective, single centre	8
Sasaki (2023)	Japan	245	n/a	n/a	1 month	16.7	3 years	BEV, SEV	n/a	n/a	Retrospective, single centre	7
Schymik (2015)	Germany	634	82/82	33/41	Hospital discharge	31.1	1 year	BEV, SEV	Log. EuroScore 21.7	n/a	Retrospective, multi-centre	8
Tomii (2022)	Switzerland	1669	81/82	43/49	1 month	20.1	1 year	BEV, SEV, MEV	STS 4.8 (cohort)	92%	Retrospective, single centre	8
Tshushima (2022)	USA	2240	80/81	41/46	Hospital discharge	17.5	1.8 (median)	BEV, SEV	STS 5.3/5.5	n/a	Retrospective, multi-centre	9
Urena (2014)	Canada	668	78/81	49/49	Hospital discharge	11.8	13 months (median)	BEV	STS 7.6/7.9	54%	Retrospective, multi-centre	9

Table 1: Studies which assessed the prognostic outcome of NOP-LBBB after TAVI.

Author (year)	Country	Total Patients	Age (years) (RBBB/no RBBB)	Male% (RBBB/no RBBB)	New persistent RBBB Definition	Incidence p-RBBB (%)	Follow-up	Valve type	Surgical risk % (RBBB/no RBBB)	Femoral access%	Study Type	NOS Bias Score
Kilkuchi et al. (2024)	Japan	407	86 / 84	17 / 32	Postoperative days 1 & 5	4.6	30-day	BEV, SEV	N/R	N/R	Retrospective, single centre	8
Tan et al. (2024)	USA	1992	83 / 81	60 / 56	Post-procedure	0.75	1 year	BEV, SEV	N/R	N/R	Retrospective, multi-centre	9
Agha et al. (2019)	USA	489	N/R	N/R	Post-procedure	2.9	1 year	N/R	N/R	62	Retrospective, single centre	7
Jorgensen et al. (2018)	Denmark	467	N/R	N/R	Post-procedure	9.6	30-day	BEV, SEV, MECH	N/R	93	Prospective, single centre	7
Rajah et al. (2021)	Saudi Arabia	170	N/R	N/R	Post-procedure	1.18	30-day	BEV, SEV	N/R	N/R	Retrospective, single centre	6

Table 2: Studies which assessed the prognostic outcome of NOP-RBBB after TAVI.

Figure Legends (Figures to follow as per Journal requirements)

Figure 1: PRISMA Diagram outlining the process of database search and study screening for both LBBB (left) and RBBB (right) arms of the review.

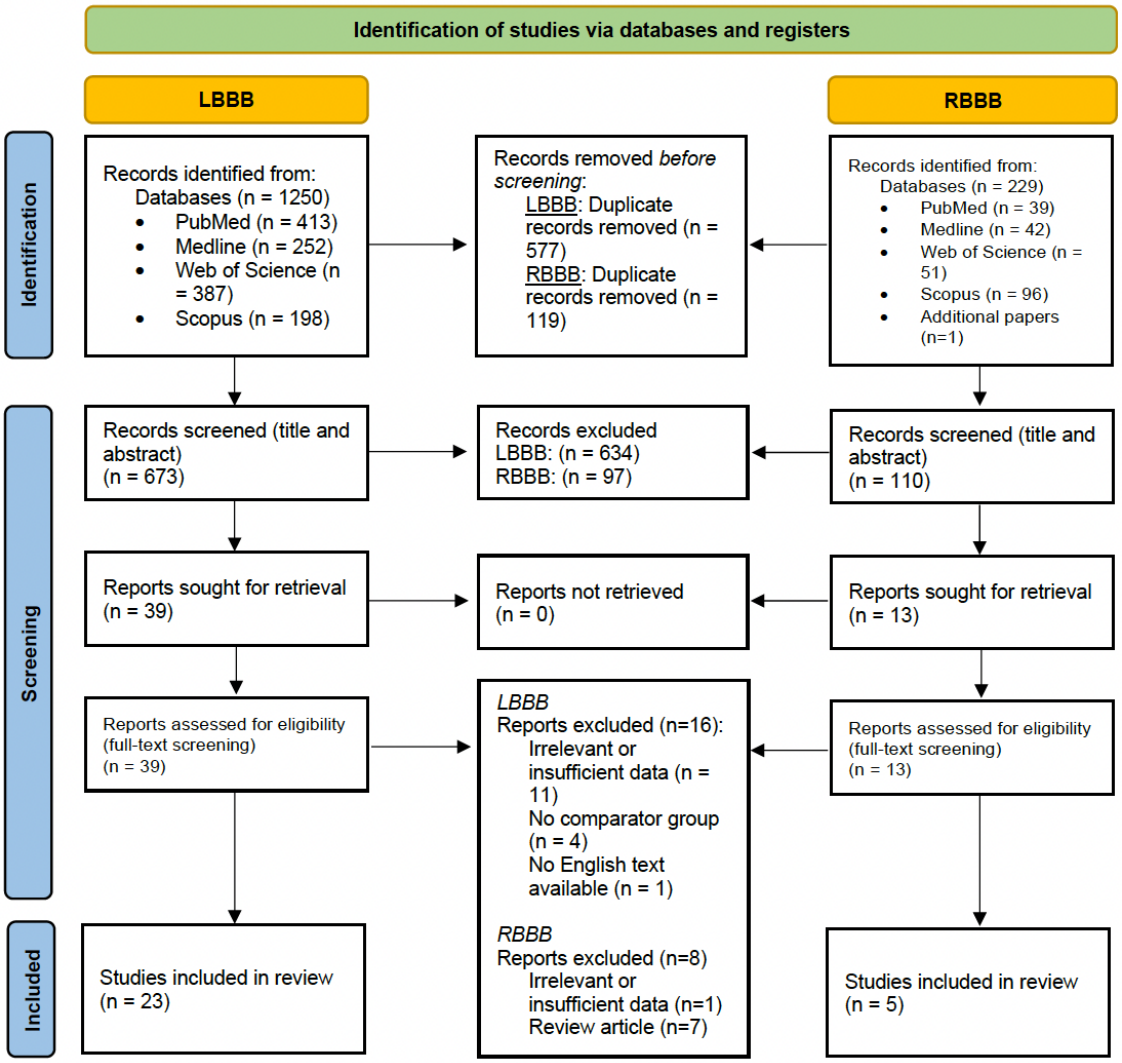
Figure 2: Figure illustrating the incidence of NOP-LBBB (%) by study year. Only studies which defined NOP-LBBB as “on hospital discharge” were included to minimise heterogeneity. The blue columns represent studies with both self-expanding (SEV) and balloon-expandable (BEV) valve use, the green columns are studies which only used BEV, whilst the maroon column used only SEV.

Figure 3: Meta-analysis of primary outcome, new onset persistent LBBB and all-cause mortality at 1 year

Figure 4: Meta-analysis of secondary outcomes of new-onset persistent LBBB

Figure 5: Meta-analysis of primary outcome of all-cause mortality at 1 year after new-onset persistent RBBB.

Figure 6: Meta-analysis of secondary outcome of new permanent pacemaker at 1 year after new-onset persistent RBBB


Identification of studies via databases and registers
LBBB
RBBB
Identification
Screening
Included
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Databases (n = 1250)
PubMed (n = 413)
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Web of Science (n = 387)
Scopus (n = 198)
Records removed before screening:
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RBBB: Duplicate records removed (n = 119)
Records identified from:
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RBBB: (n = 97)
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(n = 110)
Reports sought for retrieval
(n = 39)
Reports not retrieved
(n = 0)
Reports sought for retrieval
(n = 13)
Reports assessed for eligibility
(full-text screening)
(n = 39)
LBBB
Reports excluded (n=16):
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No comparator group (n = 4)
No English text available (n = 1)
RBBB
Reports excluded (n=8)
Irrelevant or insufficient data (n=1)
Review article (n=7)
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(full-text screening)
(n = 13)
Studies included in review
(n = 23)
Studies included in review
(n = 5)

Figure 1

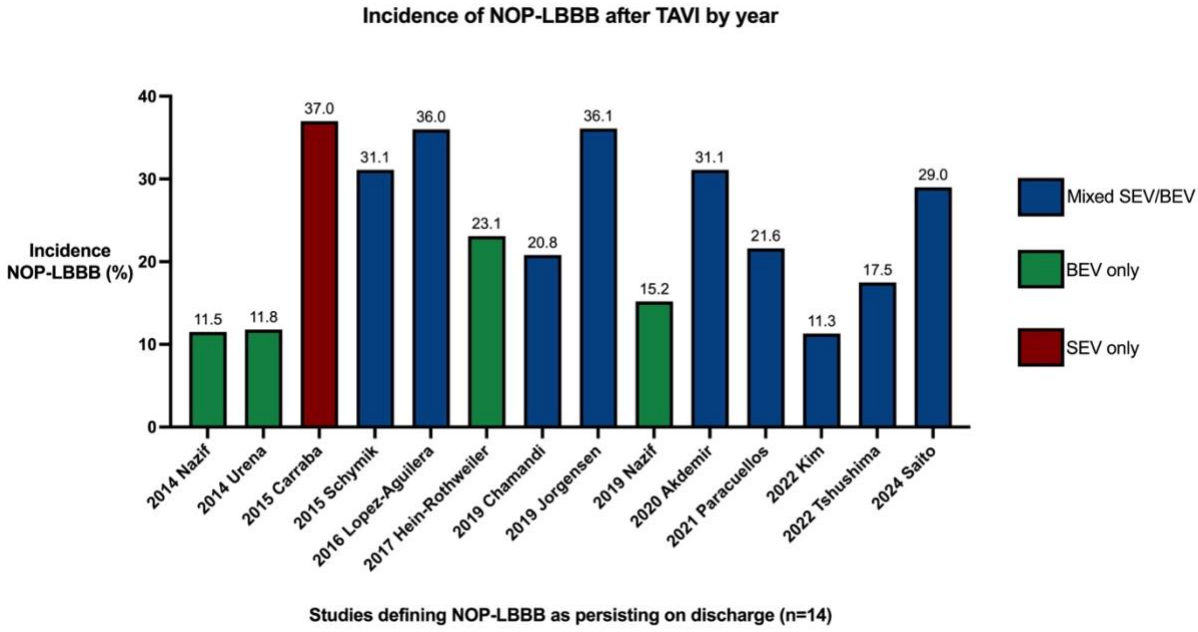


Figure 2

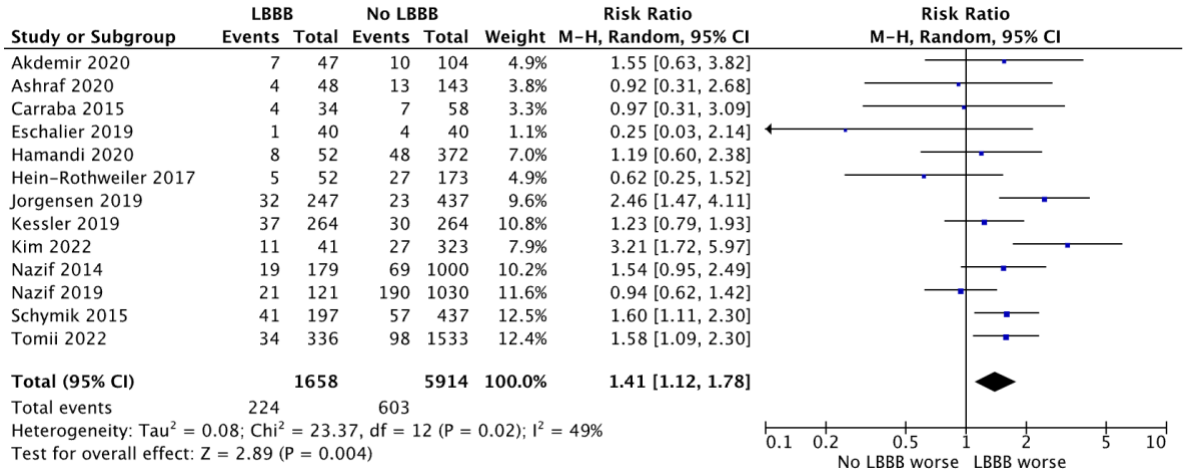


Figure 3

Figure 4

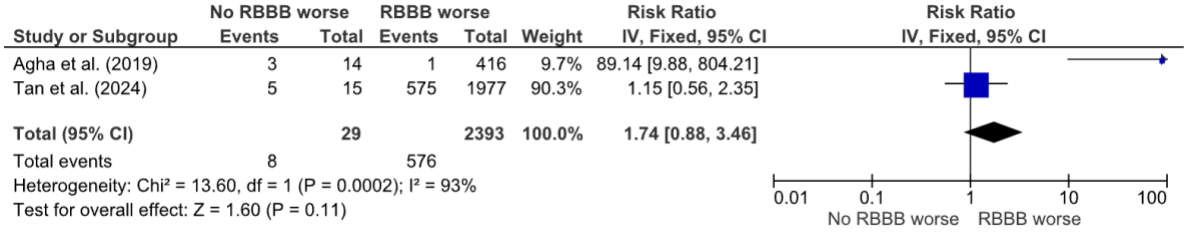


Figure 5

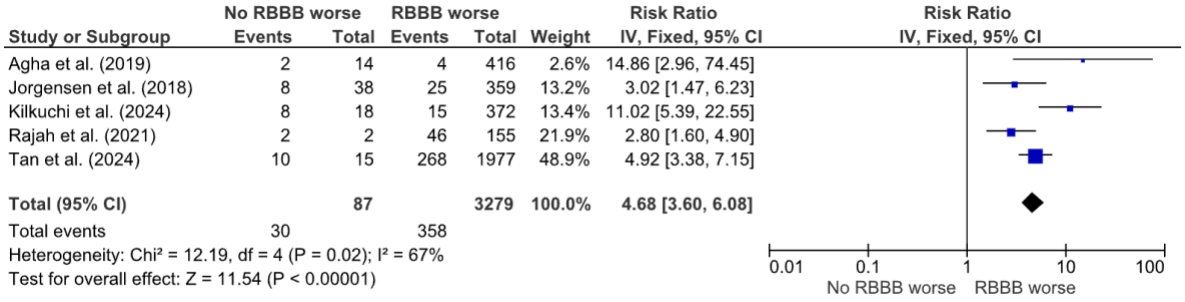


Figure 6

CHAPTER 5: Retrospective evaluation of the incidence and predictors of permanent pacemaker implantation after transcatheter aortic valve implantation

Author contribution statement:

This chapter has been submitted for peer review. It is a large retrospective evaluation of the incidence and predictors of a new pacemaker after TAVI at our local institution. I am the primary author of this work, and was involved in the study conception, ethics, data-analysis and manuscript writing. Professor Ravinay Bhindi and co-authors provided intellectual input. I take primary responsibility for the accuracy and integrity of the work presented.

Retrospective single-centre study evaluating ECG and procedural predictors of new permanent pacemaker implantation and left bundle branch block after transcatheter aortic valve implantation

Karan Rao, Alexandra Baer, Peter Hansen and Ravinay Bhindi

Manuscript text word count: 4400 (excluding references, tables, abstract)

Short Title: Predictors of new pacemaker implantation after TAVI, a retrospective two centre experience.

Correspondence to:

Professor Ravinay Bhindi

Department of Cardiology, Royal North Shore Hospital

Reserve Road, St Leonards 2065

Australia

Email: ravinay.bhindi@sydney.edu.au

5.1 Introduction

Transcatheter aortic valve implantation (TAVI) is a safe and effective treatment for patients with severe aortic stenosis(36, 37). Despite advances in implant techniques and valve engineering, high grade atrioventricular block (HGAVB) remains a common complication of TAVI, necessitating a new in-hospital pacemaker implantation (PPMI) in 10-15% of cases(155). PPMI is associated with higher long term mortality and heart-failure rehospitalisation (118), and also leads to increased financial burden on the healthcare system(156).

The mechanism of HGAVB after TAVI involves localised injury to the conduction system. The Bundle of His and proximal left bundle branch are exposed and vulnerable at the inferior margin of the membranous septum, which can be injured by an implanted valve prosthesis. Subsequently, the membranous septum length and valve implantation depth have been described as powerful predictors of HGAVB post-TAVI(47). Outside of these metrics, other known pre-procedural or procedural predictors include a baseline right bundle branch block (RBBB), use of a self-expanding valve, and significant valve oversizing(94-96).

Despite previously identified risk factors, no validated algorithm currently exists to accurately predict PPMI after TAVI. We performed a retrospective review of the demographic, ECG-based and procedural predictors of in-hospital PPMI at our institution, to evaluate currently proposed predictors of PPMI, and to provide a foundation for future targeted prospective research.

5.2 Methods

Study design and population

This is a two-centre retrospective observational study. We screened 832 consecutive patients with severe symptomatic aortic stenosis that underwent TAVI between April 2018, and May 2024 in Sydney, Australia. Patients with a prior pacemaker, defibrillator or prior aortic valve replacement were excluded (n=133). A total of 699 remained and were included for analysis. The study was reviewed and approved by the local ethics committee (see Thesis Appendix).

TAVI procedure

Pre-procedural work up included basic ECG, transthoracic echocardiography and multi-slice computed tomography angiography (TAVI-CT). All patients were presented and approved by the local structural Heart Team. Procedural sedation was used, unless general anaesthesia was deemed clinically necessary. Pre and post dilatation was at the discretion of the implanter, as was valve choice. Both self-expanding (Medtronic Evolut R, Evolut Pro, Evolut Pro Plus, Evolut FX) and balloon-expandable (Edwards Sapien 3, Sapien 3 Ultra) were commercially available during the time of the study and were implanted at the discretion of the proceduralist. Transfemoral access was the preferred access route, except in specific circumstances whereby alternative access was required.

Data collection

Data was extracted from our local health network database. The data extracted included key clinical characteristics and demographics, pre-procedure ECG features, annular sizing, procedural characteristics, as well as in-hospital, 1-month and 1-year all-cause and cardiovascular mortality. Specific measurements from CT included annular area, perimeter, and eccentricity, which was calculated as [1 - (minimum annular diameter/maximum diameter)].

Valve oversizing was tailored to valve type; for self-expanding valves it was calculated as [(prosthesis perimeter/annulus perimeter -1) x 100%] whilst for balloon-expandable valves it was calculated as [(prosthesis area/annulus area -1) x 100%].

Study outcomes

The primary aim of the study was to investigate the incidence of in-hospital PPMI, and its association with key baseline ECG anatomical and procedural predictors

Several secondary outcomes were also evaluated. This included "late PPMI" – defined as occurring after hospital discharge until 1-year follow up. Furthermore, left bundle branch block (LBBB) was documented as early (based on post-procedure ECG up to 12 hours after TAVI), and persistent LBBB (defined as detected on last ECG prior to discharge). Also, the association between in-hospital PPMI and in-hospital and 1-year mortality was also investigated.

Statistical Analysis

All statistical analyses were performed on SPSS Version 29.0 (SPSS, Chicago, IL, USA). Categorical variables were presented as numbers and percentages. Continuous variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate. Continuous data were compared using Student's *t*-test (normal distribution) or Mann–Whitney U test (non-normal distribution). Categorical data were compared using Chi-square test or Fisher's exact test. Independent predictors of in-hospital PPM were determined using binary logistic regression. Odds ratios (ORs), along with their corresponding 95%

confidence intervals (CIs), were used to report the results. Parameters with a *p*-value ≤ 0.05 in univariate analyses were included in multivariate analyses.

5.3 Results

Baseline clinical and ECG characteristics

Of the 699 patients included in the study (after exclusion of patients with prior pacemaker or defibrillator), 102 (14.6%) required an in-hospital PPM, whereas 597 (85.4%) did not require a PPM (non-PPM group). Figure 1 demonstrates the permanent pacemaker rates by year. There was a higher proportion of males in the PPM group vs. no PPM group (59.8% vs. 74.5%, p = 0.005), but otherwise, patient clinical characteristics were similar (Table 1).

On baseline ECG, the in-hospital PPM group had a higher proportion of atrial fibrillation (29.4% vs. 19.8% p=0.048), and RBBB (24.5% vs. 4.4%, p <0.001). There was no difference in the proportion of pre-existing LBBB (PPM 2.0 vs. non-PPM 6.0%, p=0.094) and first-degree atrioventricular block (PPM 12.7 vs. non-PPM 7.9%, p = 0.104) (Table 1).

Imaging characteristics

Baseline transthoracic echocardiography (TTE) characteristics were similar across groups, in terms of LVEF (%), aortic valve mean gradient (mmHg) and septal wall thickness (mm) (Table 1). Pre-procedural CT characteristics were also similar across the two groups with regards to proportion of bicuspid valves, annular eccentricity and perimeter (mm), however there was a marginally higher annulus area (mm^2) in the PPM group (496.7 vs. 471.34mm^2, p = 0.023) (Table 1).

Procedural characteristics

The type of procedure anaesthetic and vascular access were similar across in-hospital PPM and non-PPM groups (Table 2). There was a higher proportion of self-expanding valves used in the PPM group (70.6 vs. 57.5%, p =0.013), with a higher mean THV size (29.6 vs. 27.9mm, p = 0.001), and a greater mean oversizing percentage (%) (15.6 vs. 12.6%, p = 0.020). There was no difference in post or pre-dilatation frequency across the two groups. Figure 2 illustrates the pacemaker rates arranged by specific valve model used in the cohort. Patients requiring an in-hospital PPM were more likely to have a longer length of stay compared to patients in the non-PPM group (6.0 vs. 3.0 days, p<0.001) (Table 2).

Outcomes

The primary outcome of new permanent in-hospital pacemaker occurred in 102 (14.6%) of cases. Total pacemakers between discharge and 1-year, that is, "delayed" or "late" pacemakers occurred in 15 (2.1%) of the cohort. New early (<12 hours) LBBB (12 hours post-TAVI) occurred in 191 (28.6%) of cases, whereas *persistent* new LBBB (on discharge) occurred in 81 (12.3%). In-hospital (all-cause) mortality was seen in 9 (1.3%) cases (Table 3), of which 3 (2.9%) occurred in patients with an in-hospital PPM, whilst 6 occurred in the non-PPM group (p=0.109).

All-cause mortality at 1-year was observed in 47 (6.7%) in the cohort, with 11 (10.8%) occurring in the in-hospital PPM group, with 36 (6.0%) in the non-PPM group, however the difference was not statistically significant (p=0.076) (Table 3). Cardiovascular mortality at 1 year was seen in 16

(2.3%) patients, of which 14 (2.3%) occurred in the non-PPM group, whereas 2 (2.0%) occurred in the PPM group (p=0.854).

On univariable logistic regression analyses, male gender [OR 1.96 (1.22-3.15), p=0.005)], pre-existing RBBB [OR 7.13 (3.92-12.97), p<0.001)], self-expanding THV [OR 1.78 (1.13-2.80), p = 0.013)] and valve oversizing >15% [OR 1.96 (1.26-3.06), p=0.003)] were associated with in-hospital PPM. On multivariable regression analyses, male gender [aOR 1.72 (1.051-2.83), p=0.031], pre-existing RBBB [aOR 6.89 (3.70-12.81), p<0.001] and self-expanding valves [aOR 2.03 (1.25-3.29), p = 0.004)] remained independently associated with in-hospital PPM (See table 4).

There were no independent predictors of new onset LBBB (early *or* persistent) when assessed via multivariable logistic regression (see Supplementary Table 1).

5.4 Discussion

The primary findings of our retrospective study of 699 patients can be summarised as follows: (1) the incidence of new in-hospital PPM was 14.6%, and delayed PPM (30 days to 1 year) was 2.1%; (2) immediate new LBBB was seen in 28.6% after TAVI, whereas persistent new LBBB (on discharge) was noted in 12.3% after TAVI; (3) male gender, pre-existing RBBB and self-expanding valves independently predicted new in-hospital PPMI after TAVI; (5) there were no independent predictors for immediate or persistent LBBB on multivariable analysis.

The incidence of in-hospital PPM in our cohort (14.6%) was marginally higher than the recently published large STS/ACC TVT Registry, which reported an overall rate of 11.3% across 184,452 patients across 653 sites from 2016-2020 receiving either a Sapien 3 (balloon expandable) or Evolut (self-expanding) valve system. (155). Whilst patient demographics were similar, the discrepancy could be partially be explained by a greater use of self-expanding valves (59.4%) in our cohort.

We reported self-expanding valves to be independently associated with a higher PPMI, compared to balloon-expandable valves. This is consistent with prior literature (157, 158) and is believed to be due to the self-expanding prosthesis having a taller frame, with a deeper implant, with greater annular and LVOT oversizing, which imparts a greater radial force on the native conduction system. However, the varying outcomes between the valve platforms appears to be changing due to modern valve designs and more precise implantation depth with the use of the cusp-overlap (62) technique for self-expanding valves. The cusp-overlap technique advocates for valve deployment in the right anterior oblique (RAO)-Caudal fluoroscopic project which overlaps the right and left coronary cusps, thus isolating the non-coronary cusp and elongating the LVOT (and membranous septum) – thereby reducing radiographic foreshortening and parallax error. With very strict use of the cusp-overlap technique and high deployment, pacemaker rates after TAVI have been reported to be 6-9%(62) with self-expanding valves, although interestingly, was unable to be reproduced in our cohort, whereby we noted similar pacemaker rates even following adoption of the cusp overlap technique in our practice form 2022.

Our results also suggest male sex to be an independent risk factor of PPMI, which is also in line with prior results (159, 160). Currently, the mechanism behind this association is unclear, however it has been postulated that males may have a less favourable clinical profile with a greater incidence of RBBB(161), aortic regurgitation, atrial fibrillation as well as other comorbidities such as diabetic and chronic kidney disease peri-procedurally, which may facilitate the increased risk of PPMI(162).

Also consistent with published literature, pre-existing RBBB was the strongest predictor of a PPMI after TAVI in our cohort. The rate of new PPMI in patients with pre-existing RBBB has been estimated between 30-50%(163), and in our cohort, of the 51 patients with a pre-existing RBBB, 25 (49.0%) required a PPM. This risk is due to frequent prosthesis-induced injury of the superficial *left* bundle branch on the ventricular side of the LVOT. Due to the significant independent risk of PPMI in patients with a pre-existing RBBB population, it has been appropriately proposed that this group should undergo longer cardiac monitoring prior to discharge. Recently, a UK group has recommenced prophylactic pacing for *all* patients with baseline RBBB, reporting reductions in lengths of stay and rehospitalisation(164). Although this strategy still needs confirmation from prospective randomised study, it is notable that in our cohort, patients who required a PPMI remained in hospital for twice as long ($p<0.001$), with obvious implications on healthcare costs.

Valve oversizing was found to be associated with PPMI on our univariable analysis, which has been reported previously(165, 166). Managing valve oversizing can be delicate, as appropriate oversizing can aid valve anchoring and haemodynamic performance and reduce paravalvular

regurgitation(167), whereas “overshooting” can increase the risk of annular rupture and permanent pacemaker requirement. PPMI from oversizing is believed to occur due to the greater force imparted on the LVOT, and more specifically the native conduction system. Optimal oversizing is vendor specific(57, 168), as the self-expanding valves rely on perimeter-based sizing and suggests 10-15%, whereas the balloon-expandable S3 platform use an area-based measurement, as the valve is assumed to circularise, and aims for 5-10%. Our measurements factored this in to report a targeted oversizing (%) for each specific valve used.

The adverse clinical implications of a new PPMI have been well established in surgical aortic valve replacement cohorts, with poorer long-term outcomes(169). The prognostic relevance of an in-hospital PPMI or even a new persistent LBBB after TAVI has historically been unclear, with older studies reporting conflicting data(117, 170). However more recent meta-analyses(118, 171) now clearly demonstrate unequivocally higher all-cause and cardiovascular mortality, and increased heart-failure related rehospitalisation long-term follow up in patients receiving a PPMI after TAVI, similar to SAVR populations. Whilst this study was not adequately powered to investigate the prognostic impact of in-hospital PPM, there was a trend towards a greater all-cause mortality at 1 year (10.8 vs. 6.0%, $p = 0.076$). The underlying pathophysiological mechanism relates to mechanical dyssynchrony resulting in negative cardiac remodelling and reduced cardiac output. As such, the adverse impact of dyssynchrony is likely to become more pronounced with time - becoming more relevant with a shift to TAVI in low surgical risk patients, with greater life expectancy. The development of conduction system pacing may have particular utility in the post-TAVI population, to achieve shorter paced QRS intervals, and more synchronised ventricular contraction(120).

Whilst the primary outcome of this study was an in-hospital PPMI, 2.1% of the cohort required a "late" pacemaker, that is, after hospital discharge and until 1 year. Considering our results relied on registry-based data, it is possible our findings may underestimate this outcome. Importantly, delayed atrioventricular block is not as well studied or understood compared to early (or in-hospital) atrioventricular block and may be an important contributor to unexplained sudden cardiac death after TAVI. A 2021 study which used implantable loop recorder data in 59 patients up to 1 year, concluded the incidence of delayed high-grade atrioventricular block to be 11.9%(172). However, the literature remains heterogenous, with a 2023 systematic review estimating the incidence of delayed pacemakers in the literature to be between 1.7-14.6%(173). Prior studies have proposed a pre-existing RBBB and a new persistent LBBB as leading predictors for delayed pacemaker. Whilst this current study was not adequately powered to assess the predictors of delayed (out-of-hospital) PPMI, it should remain a key priority for future prospective work, as it remains to be seen whether such patients share similar risk factors to in-hospital PPMI.

Contrasting delayed presentation of atrioventricular block, a substantial number of patients may also potentially *recover* their conduction system due to improvement in transient localised inflammation(154). One study, which reviewed pacemaker evaluations at 1-year after TAVI, reported that only 33-36% patients remained dependent(174). Difficulty in predicting conduction system recovery often complicates the decision to implant a pacemaker in the early phase post-TAVI. Whilst delayed presentations of high-degree atrioventricular block can cause syncope and sudden cardiac death, an unnecessary pacemaker may cause preventable morbidity. Conduction recovery was apparent in our cohort when comparing immediate to persistent (on

discharge) new LBBB rates after TAVI. A new LBBB was seen in 28.6% early (<12 hours) which dropped to 12.3% on discharge.

The management of a persistent left bundle branch is also controversial. Recent studies have recommended measuring the His-Ventricle (HV) interval peri-procedurally to assess for abnormal infra-Hisian conduction to further stratify these patients(40, 175). Whilst LBBB has historically been considered a *benign* outcome of TAVI, recent meta-analyses have also reported poorer mid and long-term outcomes after TAVI(41, 152).

Limitations

This study was retrospectively conducted via data extracted from the local health district structural cardiology registry, which may incorporate inherent bias. Therefore, extractable data was limited to what was input, and membranous septum length as well as valve implantation depth were not available for analysis, both of which have been published to be powerful predictors of PPMI after TAVI and should be incorporated into any prospective study. As discussed above, the reason and timing for in-hospital PPM was not available, and it is possible that certain patients underwent PPMI for reasons other than high-grade atrioventricular block.

5.5 Conclusion

This retrospective review of two tertiary centres in Australia demonstrates that PPMI occurs commonly after TAVI. Independent predictors in this cohort included pre-existing RBBB, male gender and self-expanding valve use. Up to a third of patients may experience a new LBBB after TAVI, with the majority resolving prior to discharge suggesting conduction system recovery in a

significant proportion. Further prospective studies can help improve the prediction of conduction system disease, which has important implications on clinical outcomes.

5.6 Figures and Tables

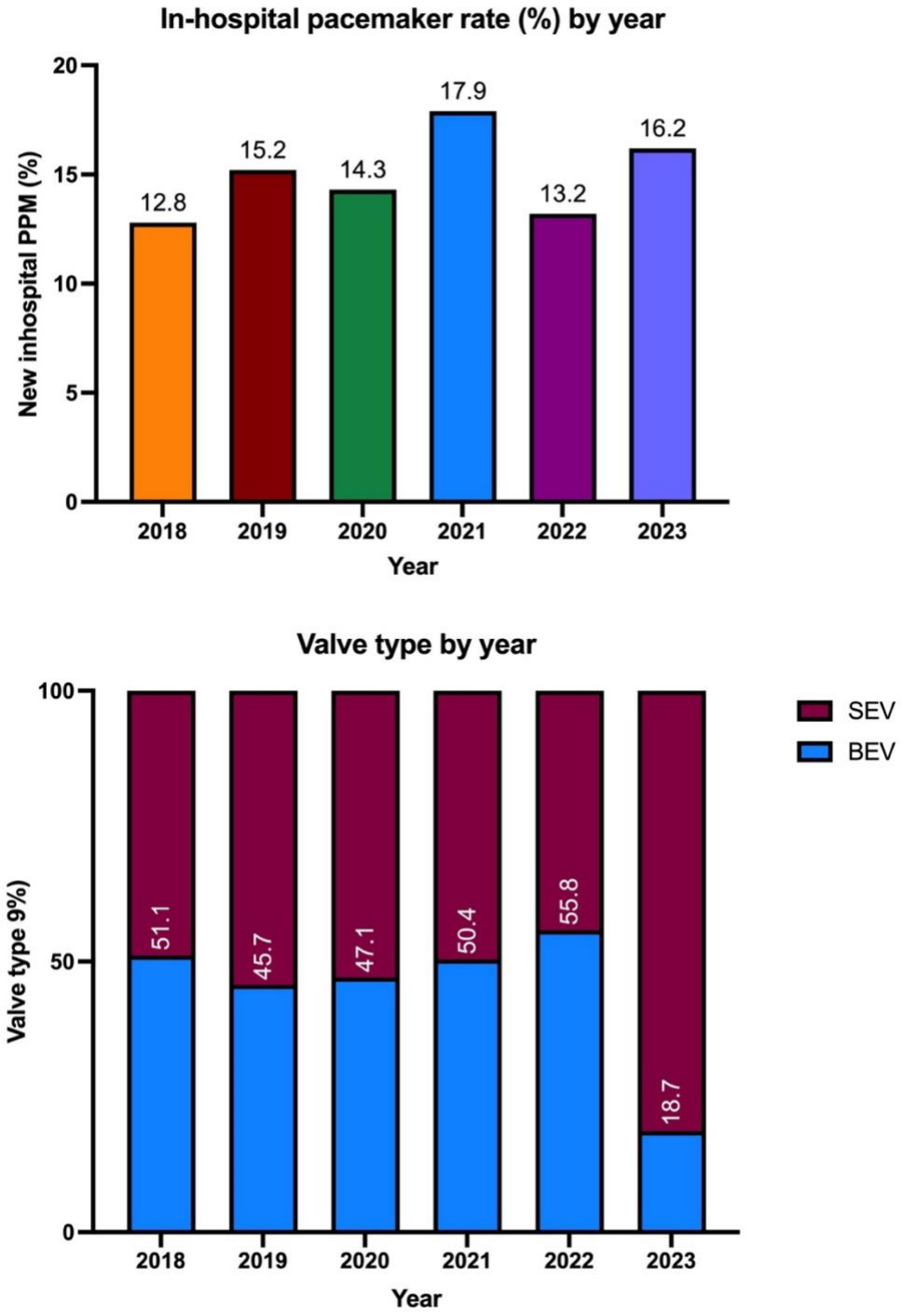


Figure 1: In-hospital pacemaker rate (%) by year (top panel); valve type by year (bottom panel).

PPM: permanent pacemaker; SEV: self-expanding valve; BEV: balloon-expanding valve. Note: these figures exclude patients with a prior cardiac device or valve surgery.

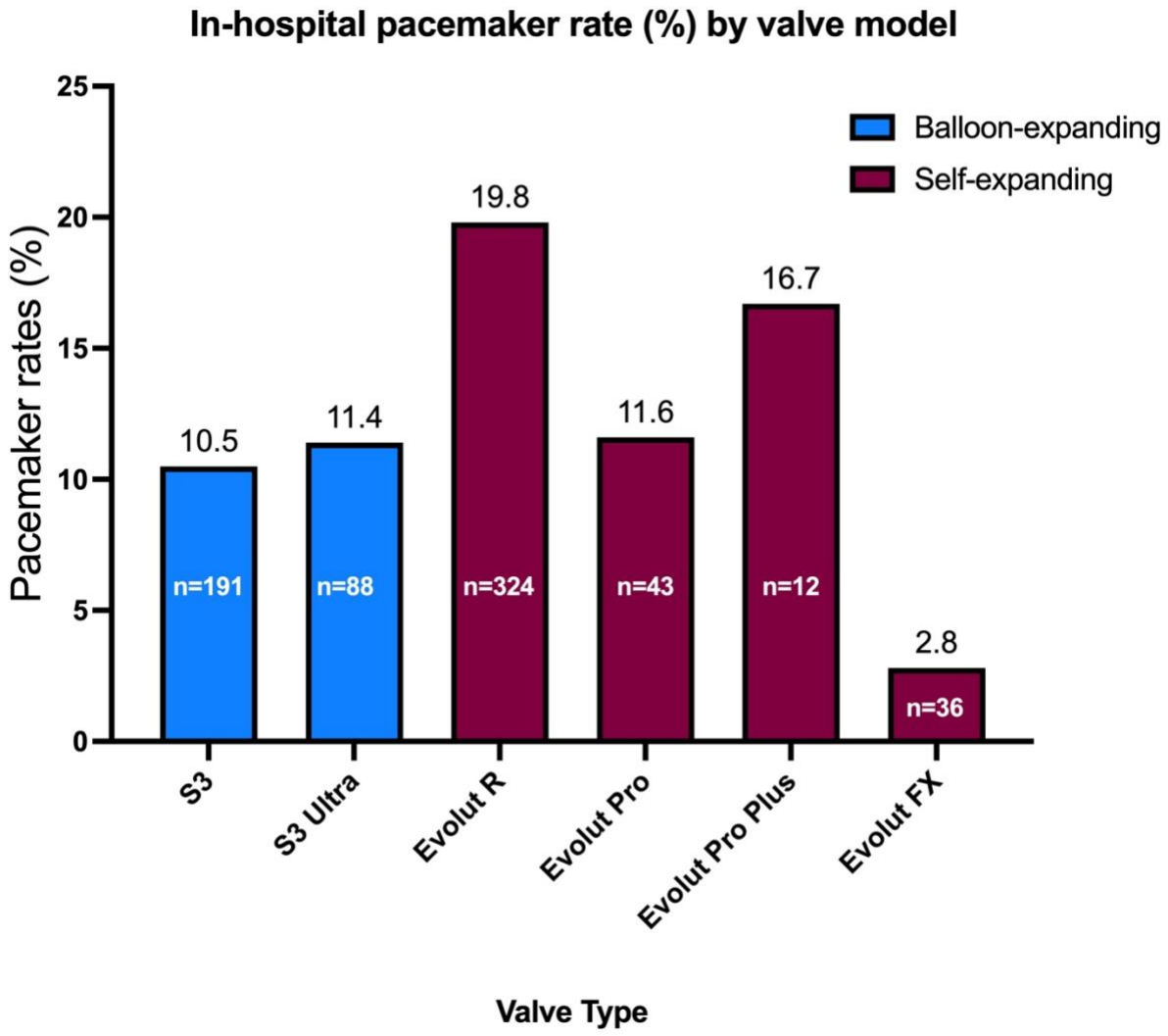


Figure 2: In-hospital pacemaker rate (%) by specific valve model
S3: Edwards Sapien 3

Tables

	All patients (n=699)	In-hospital PPM (n=102)	No PPM (n=597)	*p*-value
Baseline Characteristics				
Age (years), mean (SD)	81.9 (9.1)	82.5 (10.2)	81.8 (8.3)	0.508
Male, n (%)	434 (62.0)	76 (74.5)	368 (59.8)	**0.005**
BMI, mean (SD)	28.0 (5.9)	28.3 (5.2)	27.9 (6.0)	>0.05
Hypertension, n (%)	538 (77.0)	84 (82.4)	454 (76.0)	0.162
Diabetes, n (%)	204 (29.3)	33 (32.4)	171 (28.7)	0.459
NYHA Class >III, n (%)	520 (74.4)	86 (85.2)	434 (74.8)	>0.05
COPD, n (%)	155 (22.2)	23 (22.5)	132 (22.1)	0.763
Prior atrial fibrillation, n (%)	213 (30.6)	38 (37.6)	175 (29.4)	0.096
Prior CAD, n (%)	402 (57.5)	58 (56.9)	344 (57.9)	0.843
Prior stroke, n (%)	32 (4.6)	4 (3.9)	28 (4.7)	0.729
eGFR (ml/m^2), mean (SD)	58.1 (21.3)	58.3 (19.5)	58.1 (21.7)	>0.05
STS Score (%), mean (SD)	3.3 (2.2)	3.6 (2.1)	3.2 (2.2)	>0.05
Baseline ECG				
Atrial fibrillation, n (%)	148 (21.2)	30 (29.4)	118 (19.8)	**0.048**
RBBB, n (%)	51 (7.3)	25 (24.5)	26 (4.4)	**<0.001**
LBBB, n (%)	38 (5.4)	2 (2.0)	36 (6.0)	0.094
1st-degree AV block, n (%)	60 (8.6)	13 (12.7)	47 (7.9)	0.104
Echo				
LVEF (%), mean (SD)	57.6 (12.0)	55.6 (13.1)	58.0 (11.8)	0.088
AV Mean gradient (mmHg), mean (SD)	42.8 (14.0)	42.0 (15.8)	43.0 (13.6)	>0.05
Septal wall thickness (mm), mean (SD)	1.2 (0.4)	1.2 (0.5)	1.2 (0.3)	>0.05
CT characteristics				
Bicuspid, n (%)	35 (5.0)	6 (5.9)	29 (5.0)	0.930
Annular Eccentricity, mean (SD)	0.21 (0.06)	0.22	0.21 (0.06)	0.700
Annular perimeter (mm), mean (SD)	79.4 (27.0)	80.4 (6.8)	79.2 (29.1)	>0.05
Annular area (mm^2), mean (SD)	475.13 (100.1)	496.7 (88.03)	471.34 (101.72)	**0.023**

Table 1: Baseline characteristics

BMI: body mass index; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; STS: Society of Thoracic Surgeons; RBBB: right bundle branch block; LBBB: left bundle branch block; AV: atrioventricular; LVEF: left ventricular ejection fraction; SD: standard deviation

	All patients (n=699)	In-hospital PPM (n=102)	No PPM (n=597)	p-value
Procedural characteristics				

Anaesthetic, n (%) GA Sedation	 93 (13.3) 606 (86.7)	 16 (15.7) 86 (84.3)	 77 (12.9) 520 (87.1)	0.798
Access, n (%) Femoral Carotid Trans-Caval	 694 (99.3) 3 (0.4) 2 (0.3)	 101 (99.0) 1 (1.0) 0 (0)	 593 (99.3) 2 (0.3) 2 (0.3)	0.610
Valve Type Self-expanding, n (%) - Evolut R - Evolut Pro - Evolut Pro Plus - Evolut FX Balloon-expanding, n (%) - Sapien 3 - Sapien 3 Ultra	 415 (59.4) 324 (46.4) 43 (6.2) 12 (1.7) 36 (5.0) 284 (40.2) 196 (69.0) 88 (12.6)	 72 (70.6) 64 (62.7) 5 (4.9) 2 (2.0) 1 (1.0) 30 (29.4) 20 (19.6) 10 (9.8)	 343 (57.5) 260 (43.6) 38 (6.4) 10 (1.7) 35 (5.9) 254 (42.5) 176 (29.5) 78 (13.1)	**0.013**
THV Size (mm), mean (SD)	28.2 (3.7)	29.6 (3.5)	27.9 (3.6)	**0.001**
Oversizing (%), mean (SD)	13.0 (14.8)	15.6 (15.3)	12.6 (10.6)	**0.020**
Pre-dilatation, n (%)	81 (11.9)	10 (10.0)	71 (12.2)	0.534
Post-dilatation, n (%)	43 (6.9)	4 (4.3)	39 (7.3)	0.285
Hospital length of stay, days, median (IQR)	3.0 (4.0)	6.0 (6.0)	3.0 (3.0)	<0.001

Table 2. Procedural characteristics

GA: general anaesthetic; THV: transcatheter heart valve; IQR: interquartile range; SD: standard deviation

Outcomes	All patients (n=699)	In-hospital PPM (n=102)	No PPM (n=597)	p-value
Primary				
In-hospital PPM, n (%)	102 (14.6)	n/a	n/a	-
Secondary				
Late (Discharge to 1-year) PPM, n (%)	15 (2.1)	n/a	n/a	-
New LBBB immediate post TAVI, n (%)	191 (28.6) *n=661 (excluding prior LBBB)	n/a	n/a	-
New LBBB on discharge (persistent), n (%)	81 (12.3) *n=661 (excluding prior LBBB)	n/a	n/a	-
In-hospital mortality, n (%)	9 (1.3)	3 (2.9)	6 (1.0)	0.109
In-hospital cardiovascular mortality, n (%)	7 (1.0)	1 (1.0)	6 (1.0)	0.982

Discharge to 1-year mortality, n (%)	38 (5.4)	8 (7.8)	30 (5.0)	0.310
Discharge to 1-year cardiovascular mortality, n (%)	9 (1.3)	1 (1.0)	8 (1.3)	0.766
Total all-cause mortality at 1 year	47 (6.7)	11(10.8)	36 (6.0)	0.076
Total CV mortality at 1 year	16 (2.3)	2 (2.0)	14 (2.3)	0.854

Table 3. In-hospital, 30-day and 1-year outcomes

LBBB: left bundle branch block

Variable	OR (Univariable) (95% CI)	*P*-value	OR (Multivariable) (95% CI)	*p*-value
Age	1.01 (0.98-1.04)	0.442	1.02 (0.99-1.05)	0.257
Male Sex	1.96 (1.22-3.15)	**0.005**	1.72 (1.05-2.83)	**0.031**
Pre-existing RBBB	7.13 (3.92-12.97)	**<0.001**	6.89 (3.70-12.81)	**<0.001**
Pre-existing LBBB	0.31 (0.07-1.32)	0.112	N/A	
Pre-existing AF	1.45 (0.94-2.25)	0.107	N/A	
Pre-existing Type 1 AV block	1.71 (0.89-3.29)	0.108	N/A	
Self-expanding THV	1.78 (1.13 – 2.80)	**0.013**	2.03 (1.25-3.29)	**0.004**
Valve size	1.13 (1.07-1.19)	**<0.001**	N/A*	
Oversizing >15%	1.96 (1.26-3.06)	**0.003**	N/A*	

Table 4. Logistic regression analyses on predictors for in-hospital PPM in patients undergoing TAVI using both a univariable and multivariable model. Note: patients with p-value <0.1 were included in multivariable analysis. The multivariable model consisted of Age, Gender, Pre-existing RBBB and self-expanding THV.

OR: odds ratio; CI: confidence interval; RBBB: right bundle branch; LBBB: left bundle branch; AF: atrial fibrillation; AV: atrioventricular; THV: transcatheter heart valve

**Note: valve size / oversizing was not included in the multivariable regression due to collinearity with valve type (self-expanding valves have a higher recommended targeted oversizing %).*

Supplementary Table

	Immediate LBBB after TAVI		Persistent new onset LBBB after TAVI (discharge)	
Variable	OR (multi-variable) (95% CI)	*p*-value	OR (multi-variable) (95% CI)	*p*-value
Age	1.02 (0.99-1.04)	0.187	1.00 (0.97-1.03)	0.997
Female Sex	1.21 (0.79-1.84)	0.377	1.00 (0.55-1.82)	0.992
Pre-existing AF	0.75 (0.51-1.09)	0.130	1.34 (0.81-2.20)	0.254
Pre-existing Type 1 AV block	0.68 (0.36-1.31)	0.249	0.94 (0.39-2.31)	0.898
Self-expanding THV	1.10 (0.58-2.09)	0.774	1.77 (0.71-4.42)	0.220
Valve size	0.99 (0.92-1.06)	0.728	1.00 (0.91-1.10)	0.996
Oversizing >15%	1.19 (0.67-2.13)	0.555	1.27 (0.57-2.82)	0.563

Supplementary Table 1. Univariable logistic regression analyses on predictors for immediate and persistent new-onset LBBB after TAVI. [Supplementary].

OR: odds ratio; CI: confidence interval; AF: atrial fibrillation; AV: atrioventricular; THV: transcatheter heart valve

CHAPTER 6: Prospective observational study evaluating the incidence and predictors of high-grade atrioventricular block after transcatheter aortic valve implantation (CONDUCT-TAVI)

Circulation: Cardiovascular Interventions
New online
https://doi.org/10.1161/CIRCINTERVENTIONS.125.015446

ORIGINAL ARTICLE

Prospective Observational Study on the Accuracy of Predictors of Permanent Pacemaker Secondary to High-Grade Atrioventricular Conduction Block After TAVI (CONDUCT-TAVI)

Karan Rao, BMed, MD, MPH, Bernard Chan, MBBS, Kunwardeep Bhatia, MBBS, Natasha Saad, BSc, MClinExPhys, Alexandra Baer, BSN, MSHM, David Whalley, MBBS, PhD, Christopher Choong, MBBChir, PHD, Peter Hansen, MBBS, PhD, and Ravinay Bhindi, MBBS, PhD

Published in:

Circulation: Cardiovascular Interventions. Online, ahead of print, September 15, 2025.

Presented at:

1. Preliminary findings
    a. PCR London Valves Conference 2024 (Research Abstract Session)
    b. Australia and New Zealand Endovascular Therapies Conference (2024), Early Career Research Award Prize Session (Winner)
    c. University of Sydney, Kolling Institute Research Meeting (2024), Best Oral Presentation Winner (Winner)
2. Complete findings
    a. Cardiac Society of Australia and New Zealand Annual Scientific Meeting Ralph Reader Clinical Prize Session (Winner)

Author contribution statement:

This is the primary prospective study of my PhD. I was involved in ethics submission and subsequent amendments. I then carried out consent and recruitment for all patients (n=200). During their procedure, I conducted the electrophysiology study and analysed dedicated imaging scans. Post-procedure, I inserted implantable loop recorders in all relevant patients and then organised and performed periodic follow up for all participants. I collected the data, performed all statistical analyses and interpretation. I also wrote the final manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Prospective observational study on the accuracy of predictors of permanent pacemaker secondary to high-grade atrioventricular conduction block after TAVI (CONDUCT-TAVI)

Karan Rao BMed, MD, MPH[1, 2, 3], Bernard Chan MBBS[1], Kunwardeep Bhatia MBBS[1], Natasha Saad BSc, MClinExPhys[1], Alexandra Baer BSN, MSHM[2], David Whalley MBBS, PhD[1,2], Christopher Choong MBBChir, PHD[1,2], Peter Hansen MBBS, PhD[1, 2] & Ravinay Bhindi MBBS, PhD[1, 2, 3]

[1] Royal North Shore Hospital, Sydney, Australia

[2] North Shore Private Hospital, Sydney, Australia

[3] University of Sydney, Australia

Corresponding author:

Professor Ravinay Bhindi

Royal North Shore Hospital, Reserve Road, St. Leonards, 2065.

Email: ravinay.bhindi@sydney.edu.au, Phone: (02) 9926 7111

Short Title: CONDUCT-TAVI

Word count: 7273 (all inclusive)

Acknowledgements: Dr. Hari Sritharan (assistance in conceiving the study protocol); Dr. Neila Litkouhi (assistance in aspects of data collection). Ms. Ingrid Bromhead (assistance in screening for recruitment).

Ethics: Northern Sydney Local Health District Ethics Committee

6.1 Abstract

Background

The incidence of permanent pacemaker implantation (PPMI) due to high-grade atrioventricular block (HGAVB) after transcatheter aortic valve implantation (TAVI) is 10-15% at one-year, and current prediction algorithms remain unreliable.

Methods

CONDUCT-TAVI is a prospective observational study of 200 patients undergoing TAVI across two centres. Baseline demographic, anatomical and procedural characteristics were recorded, followed by targeted electrophysiology studies (EPS) and continuous rhythm monitoring using implantable loop recorders for 1-year. The primary outcome was PPMI secondary to HGAVB, and secondary outcomes included early (≤48 hours) and late (>48 hours) PPMI, new-onset persistent left bundle branch block (LBBB), and new-onset atrial fibrillation (NOAF). Predictors were assessed using multivariable logistic regression.

Results

PPMI due to HGAVB occurred in 21.0% of patients (early PPMI: 13.5%, late PPMI: 7.5%). Key predictors included pre-existing right bundle branch block (RBBB) [aOR 5.45 (1.67-17.84), p=0.005], ΔHV interval >10 ms [aOR 3.62(1.23-10.67), p=0.020], and pre-TAVI rapid atrial pacing-induced AV Wenckebach [aOR 3.70(1.37-9.98), p=0.010]. The CONDUCT-TAVI score combined these variables with high predictive accuracy (AUC=0.794) and negative predictive value (98%). New-onset persistent LBBB (>24 hours) was observed in 19.1%, and NOAF in 21.7% at one-year.

Conclusion

The incidence of conduction abnormalities remains high after TAVI, and after factoring anatomical, procedural and electrophysiological factors, a baseline RBBB and EPS derived measures of AV conduction were the most significant predictors of PPMI. The CONDUCT TAVI Score incorporates these findings to help implanters stratify low risk patients and tailor follow up care.

Keywords: TAVI; atrioventricular block; permanent pacemaker; electrophysiology study; left bundle branch block; atrial fibrillation

What is known?

- Despite advancements in valve engineering and implantation techniques, high-grade atrioventricular block (HGAVB) requiring permanent pacemaker implantation is still prevalent after transcatheter aortic valve implantation, believed to occur in up to ~15% of all cases.
- There is a lack of a reliable and reproducible prediction algorithm, despite various anatomical, procedural, and electrophysiological risk factors.

What the study adds?

- Continuous rhythm monitoring using an implantable loop recorder over one year revealed that HGAVB requiring a permanent pacemaker occurs in 21.0% of patients, with nearly over a third (7.5%) developing it after 48 hours.
- A significant number of patients (21.5%) were diagnosed with new-onset atrial fibrillation, predominantly in a paroxysmal form with varying burdens.
- The CONDUCT-TAVI Score, which includes electrophysiologically derived parameters such as pre-existing right bundle branch block, changes in HV interval, and pre-TAVI rapid atrial pacing-derived AV Wenckebach, showed high predictive accuracy and a negative predictive value of 98% for new pacemaker implantation at one year, thereby assisting implanters in patient stratification for rapid discharge.

6.2 Introduction

Post-procedural high-grade atrioventricular conduction block (HGAVB) is a common complication of TAVI, primarily due to the proximity of the membranous septum to the aortic valve complex. This leaves the Bundle of His and left bundle branch vulnerable to injury, with new permanent pacemaker implantation (PPMI) occurring in 10-15% and persistent left-bundle branch block (LBBB) in 20-25%(176, 177). Both conditions are linked to adverse patient outcomes at long-term follow up(171, 178).

Several anatomical factors may contribute to post-TAVI conduction disease, including severe calcification, a short membranous septum, and a tapering left ventricular outflow tract (LVOT). Procedural risk factors include self-expanding valves, deep implantation, and oversizing (>20%). Electrophysiological predictors include pre-existing right bundle branch block (RBBB), post-procedural PR interval prolongation, or the emergence of any new bundle branch block, and recently, periprocedural electrophysiology studies (EPS) have helped in evaluating His Bundle conduction, by measuring the HV interval(68) and implementing rapid atrial pacing to assess the AV Wenckebach cycle length(69). Despite numerous risk factors, a reliable predictive algorithm for PPMI post-TAVI is still lacking.

HGAVB typically occurs within 48 hours post-TAVI but occurs late (>48 hours) in 2-14%(172, 173). Late HGAVB often arises after discharge and may contribute to unexplained sudden cardiac death, although its underlying mechanisms and risk factors require further investigation. Additionally, new-onset atrial fibrillation (NOAF) after TAVI can increase mortality, rehospitalisation, stroke rates, bleeding, and PPMI(179), with an incidence estimated at 10% at

1-year(73). As the trend shifts toward early discharge after TAVI, accurately identifying and stratifying arrhythmias is essential for improving and streamlining follow-up care.

6.3 Methods

CONDUCT-TAVI (ACTRN12621001700820) is an Australian prospective observational study, and the rationale and design has been previously described(180). The study has been approved by the local ethics committee, all participants provided informed consent, and amendments to the protocol were submitted to the committee prior to implementation (notably a reduction in follow-up length to from two years to one). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Consecutive elective transfemoral TAVI were screened (2021-2023) during the institutional structural Heart Team meeting and were excluded if they had a prior pacemaker, defibrillator or prior aortic valve surgery. All study participants provided written informed consent.

Pre-procedural imaging

Prior to the planned TAVI, all patients underwent routine transthoracic echocardiography, and ECG-gated multidetector computer tomography (CT-TAVI)

CT-TAVI images were reviewed independently offline using specialised software (3Mensio imaging software, Pie Medical Imaging, Netherlands). During peak ventricular systole, valve morphology (bicuspid versus tricuspid), annular and left ventricular outflow tract (LVOT)

dimensions, and coronary cusp calcium volumes at the device landing zone (DLZ) were recorded. The DLZ was defined as a 15mm segment encompassing 10mm above and 5mm below the annular plane (Supplementary Figure 1). Separately, the infra-annular membranous septum length (IA-MSL) was obtained using a previously validated technique(49). The IA-MSL was measured by a single observer and averaged over three separate measurements.

TAVI Procedure details

TAVI procedures were conducted at two centres. All cases were transfemoral, under conscious sedation, with ultrasound-guided vascular access. The balloon-expandable Sapien (S3/S3 Ultra, Edwards Lifesciences, Irvine, USA) as well as the self-expandable Evolut (Evolut R/Pro/Pro Plus/FX, Medtronic, Dublin, Ireland) were used at the discretion of the implanter. The Cusp Overlap technique(90) for the self-expandable platform and the High Deployment Technique(63) for the balloon-expandable platform were used. Implantation depth was measured fluoroscopically from the nadir of the non-coronary cusp in a co-planar (three-cusp or two-cusp) view as described in prior studies(49, 63).

Electrophysiology study

Targeted EPS was conducted using a dedicated multi-polar catheter (BIOTRONIK, Berlin, Germany) inserted via the right femoral vein and externally connected to a mobile electrophysiology system (Supplementary Figures 2 & 3). The His signal was measured by positioning the catheter at the septal aspect of the tricuspid annulus and defined as the intervening signal between the atrial and ventricular signal. The AH interval was measured from the onset of the atrial signal to the earliest His signal on the His bundle recording. The HV

interval was defined as the earliest His signal to the earliest ventricular signal on the surface ECG. Measurements were required to be reproducible (± 2ms) over at least 3 cardiac cycles.

Right atrial pacing (RAP) was performed using the method described by Krishnaswamy *et al.*(69), which involved pacing at heart rates from 70-120 beats per minute (bpm) in 10 bpm increments until AV Wenckebach block (Mobitz I) was observed (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 was above 70 bpm, pacing was commenced at the next increment. Patients with AF or CHB did not undergo RAP.

Continuous rhythm monitoring

Patients *without* a permanent pacing requirement underwent loop recorder implantation (ILR) prior to discharge (BIOMONITOR III, BIOTRONIK, Berlin, Germany). ILRs were programmed to detect bradycardia below 40 beats per minute, pauses over 3 seconds and tachycardia above 180 beats per minute, along with irregular heart rates. CardioMessenger Home Monitoring (BIOTRONIK, Berlin, Germany) was reviewed daily by the study team. All arrhythmias were co-reported by a cardiac technologist and electrophysiologist. NOAF was defined as at least 30 seconds of irregular R-R activity, without detectable organized atrial activity. Clinically relevant arrhythmias were referred to the treating cardiologist for management (for examples see Supplementary Figures 4 & 5)

Follow up and endpoints

All patients were followed up for 1 year. In exceptional circumstances, remote follow up was conducted via telephone. Supplementary Table 1 provides details on the CONDUCT-TAVI patient schedule. The primary study endpoint was the binary occurrence of new PPMI due to HGAVB within one year of TAVI. The decision to implant a pacemaker was left to the treating team, and the results of the EP study or volumetric calcium analysis were not used to dictate management. Secondary endpoints included time-to-event (PPMI due to HGAVB, early (≤48 hours) and late (>48 hours to 1 year) PPMI, as well as new onset persistent LBBB (≥24 hours), and NOAF.

Sample size and statistical analysis

The sample size was determined using the Wilson Interval method to calculate a two-sided 95% confidence interval with a specified width of 0.15. The estimated one-sample sensitivity was 0.98, while the prevalence of the primary outcome was projected at 0.15. Based on these parameters, a required sample size of 194 was calculated. Considering a projected drop-out rate of 5%, a total enrolment sample size of 205 was proposed. These calculations were conducted with the assistance of a biostatistician using PASS (Power Analysis and Sample Size Software) Version 20.0.3.

Continuous variables were presented as mean ± standard deviation (SD) if data were normally distributed, or median with interquartile range (IQR) if data was not normally distributed, while categorical variables were reported as percentages. Normality was assessed using the Shapiro-Wilk test. We used Fisher's Exact tests for categorical variables, and Mann-Whitney (Wilcoxon rank-sum) (non-normal distribution) or Student's t-test (normal distribution) for continuous

variables. Logistic regression assessed the relationship between variables and the primary endpoint. Variables with p-values <0.10 in univariate analyses were included in multivariable models to reduce the risk of Type II error which may lead to a failure to detect a true association. Collinearity was assessed using correlation matrices, variable inflation factors (VIF) and clinical judgement, and was managed by selecting a variable from collinear groups based on a combination of the statistical strength of association, likelihood ratio and clinical relevance or applicability. Similarly, a Kaplan-Meier and Cox-Regression secondary analysis was also performed using time-to-event (new PPMI secondary to HGAVB). Odds Ratios (OR) and Hazard Ratios (HR) and 95% confidence intervals (CIs) were calculated. Significance was set at $p<0.05$. Analyses were performed using SPSS Version 29.0 (IBM, Armonk, NY).

6.4 Results

Study Population and clinical characteristics

From October 2021 until December 2023, 354 consecutive elective transfemoral patients underwent TAVI at the two centres recruiting for this study. Of these, 143 patients were excluded, and 11 patients withdrew, with 200 patients included in the study (Figure 1). The baseline characteristics and pre-procedural echocardiography parameters were similar across PPMI and non-PPMI groups and are described in Table 1.

CT-TAVI and procedural characteristics

Table 1 also highlights the CT and procedural characteristics of the two cohorts. The no PPMI group had a longer membranous septum length compared to PPMI group (3.1 vs. 2.0mm, p=0.003). No differences were seen in total or differential calcium volume, or annular ellipticity.

In the PPMI group, there was a greater proportion of self-expanding valves used (78.6 vs. 57.0%, p=0.01) (Table 1), whilst annular (19.7 vs. 14.8%, p=<0.001) and LVOT oversizing percentage (19.3 vs. 14.5%, p=0.007) was higher. The absolute implant depth was not different, however the calculated implant depth subtracted by the membranous septum length (ID-MSL) (mm) was lower in the PPMI group (-1.84 vs. -0.45mm, p = 0.004). Transient CHB was more common in the PPMI group (54.8 vs. 10.8%, p<0.001). There was no difference in length of stay across the groups.

ECG and EPS characteristics

On baseline pre-TAVI ECG (Table 2), the PPMI cohort had longer QRS length (108.0 vs. 88.0ms, p<0.001), and higher proportion baseline RBBB (40.5 vs. 8.8%, p<0.001). On immediate post-TAVI ECG (0 hours), the PPMI cohort had longer QRS duration (152.0 vs. 132.0ms, p<0.001), and greater proportion of both LBBB (52.9 vs. 44.0%, p=0.005) and RBBB (37.0 vs. 10.3%, p=0.035). At 4 hours post TAVI, the PR interval (207.8 vs. 190.2ms, p=0.016) and QRS intervals (152.0 vs. 112.0ms, p<0.001) were longer in the PPMI group, with a higher proportion of RBBB (39.1 vs. 9.0%, p=0.007). The QRS interval remained longer at 24 hours in the PPMI group (150.0 vs. 101.0ms, p<0.001), although no other differences were observed.

All patients underwent AH and HV interval measurement, whilst 80.5% of the cohort underwent RAP to induce AV Wenckebach (Table 2). AV Wenckebach was more commonly induced in the PPMI cohort pre- (56.3 vs. 21.9%, p<0.001), and post-TAVI (64.7 vs. 24.2%, p<0.001). No difference was observed in AH and HV intervals, however the ΔHV interval was longer in PPMI group (14.0 vs. 6.0ms, p=0.005).

Primary outcome and other clinical outcomes

42 patients (21.0%) reached the primary outcome of new PPMI due to HGAVB (Table 3). Of these, 27 (13.5% of total cohort) were inserted ≤48 hours (early PPMI) whilst 15 (7.5% of cohort) required PPMI >48 hours (late PPMI). 6 (3.0%) patients received PPMI due to reasons unrelated to AV block (sick sinus syndrome, or tachy-brady syndrome). Median time to PPMI was 1.5 (±16.0) days, and the median time in the *late* PPMI cohort was 37 (±87.0) days (Table 4). Freedom from PPMI secondary to HGAVB is illustrated in Figure 2, whilst the indications and long-term pacing requirements are reported in Supplementary Table 2.

The incidence of new-onset LBBB immediately after TAVI was 43.6%, and 19.1% at 24 hours. New-onset LBBB at ≥ 30 days was 20.7%. NOAF was detected in 30 of the 138 (21.7%) patients without known history of AF (Table 3) with median time to diagnosis being 20.5 (±68.0) days. As explored in Table 4, among participants with NOAF, 28 individuals (93.3%) were initiated on anticoagulation therapy. The status of AF varied, with 4 (13.3%) remaining in persistent AF at the 1-year follow-up, whilst the remainder (86.7%) remained in paroxysmal AF. NOAF was detected peri-procedurally (Day 0) in 3 individuals (10.0%), while 7 individuals (23.3%) were diagnosed within the first week (Days 1-7). The remaining 20 individuals (66.7%) were diagnosed after the first week, continuing until the 1-year mark

Other clinical outcomes are also represented in Table 3. 15 (7.5%) patients died at 1 year, of which 5 (2.5%) were due to a cardiovascular cause. The rate of cardiovascular rehospitalization was 17.0%, and major vascular complication or bleeding was seen in 4.0%. There were 13 (6.5%) strokes (or TIA), and 3 (1.5%) cases infective endocarditis.

Logistic Regression

Table 5 lists the univariable and multivariable logistic regression of pre-specified predictors of PPMI. Collinearity was managed by selecting a single variable based on statistical and clinical relevance (for further details on management of collinearity see Supplementary Table 3). Pre-existing RBBB [aOR 5.45 (95% CI 1.67-17.84), p = 0.005], ΔHV>10 (or CHB) [aOR 3.62 (95% CI 1.23-10.67), p = 0.020] and pre-TAVI RAP induced AV Wenckebach [aOR 3.70 (95% CI 1.37-9.98), p = 0.010] were independently associated with permanent pacemaker implantation at 1 year.

The regression co-efficients (Table 5) of these independently significant variables were used for risk score development which resulted in an area under the curve (AUC) of 0.802 (95% CI 0.731-0.874) (Supplemental Figure 5). Subsequently, a simplified version of the model: 1 point for pre-existing RBBB, 1 point for ΔHV>10 (or CHB), and 1 point for Pre-TAVI RAP induced AV Wenckebach, was found to perform similarly (AUC 0.794 95% CI 0.722-0.865; Figure 3) and was used to form the CONDUCT TAVI Score (Figure 3). The score distribution is presented in Figure 3, and a score of 0 (38.0% of the cohort) carried a sensitivity of 95%, and negative predictive value of 98% for PPMI at 1 year. The score performed similarly across both valve types used (p=0.307) (Figure 4).

On Cox regression analyses (secondary analyses) (Supplementary Table 4), pre-existing RBBB [aOR 4.35 (95% CI 1.23-14.12), p = 0.014] and pre-TAVI RAP induced AV Wenckebach [aOR 4.51 (95% CI 1.57-12.96), p = 0.005] remained independently significant on multivariable assessment. Other secondary outcomes included early and late PPMI, as well as persistent LBBB

(Supplementary Table 5). Pre-existing RBBB remained the strongest predictor regardless of PPMI timing. RAP induced AV Wenckebach was also associated with both early and late PPMI. Membranous septum length, ΔPR interval, periprocedural CHB, self-expanding valves and oversizing percentage were associated with early but not late PPMI. Post-procedure HV prolongation was associated with only late PPMI. Otherwise, implantation depth and ΔPR interval were associated with persistent LBBB.

6.5 Discussion

CONDUCT-TAVI is the first prospective study to combine demographic, anatomical, electrophysiological and procedural predictors of PPMI, coupled with continuous rhythm monitoring follow-up to 1 year. Key findings included: 1) the incidence of new PPMI resulting from HGAVB was 21.0% at one-year, with 13.5% occurring within the first 48 hours and 7.5% after 48 hours; 2) new persistent LBBB was observed in 19.1%, and NOAF in 21.7% at one year post-TAVI; 3) the independent predictors of PPMI identified were pre-existing RBBB, ΔHV>10ms (or CHB), and pre-TAVI RAP induced AV Wenckebach block, which formed the CONDUCT-TAVI Score that had negative predictive value of 98%.

PPMI secondary to high-grade atrioventricular block

The incidence of PPMI at 1-year after TAVI has varied, with the PARTNER (balloon-expandable) and Evolut (self-expanding) low-risk cohorts reporting rates of 7.5 and 19.4% respectively(138, 158). Recent non-industry sponsored mixed-valve studies, DEDICATE(176) and UK-TAVI(177), reported rates of 11.8% and 14.2% respectively. We observed a higher incidence (21.0%) which may partly reflect enhanced HGAVB detection via implanted loop recorders. We noted 7 (3.5%) patients to have transient late *asymptomatic* HGAVB (Supp. Table

2) treated with PPMI, in accordance with current European(181) and American(182) guidelines which advocate for permanent pacing (Class 1) in permanent *or* paroxysmal second-degree Mobitz Type II or complete atrioventricular block (HGAVB), regardless of symptom status.

Conduction system recovery after TAVI is variable and challenging to predict. A 2021 meta-analysis reported over 50% of patients were no longer pacing dependant at 1-year(183), aligning with our observation that 31% of patients had <10% ventricular pacing at extended follow up (Supp. Table 2). Similarly, whilst immediate new LBBB occurred in 43.6%, it persisted at 24 hours in only 19.1%. Whilst these findings caution against premature pacemaker implantation, HGAVB often presents transiently and therefore a low pacing percentage may not necessarily reflect a healed conduction system.

Importantly, not all post-TAVI bradyarrhythmia are caused via valve-induced injury. Historically, severe calcific aortic stenosis has been shown to *independently* prolong AV conduction, secondary to calcium infiltration or fibrosis(9, 10). Urena *et al*. (2015)(184) reported HGAVB occurred in 5.5% of patients monitored the day prior to TAVI. In our single-arm post-TAVI design, the proportion of patients with pre-existing conduction disease is difficult to estimate.

RBBB is a well-known risk factor, since mechanical valve-induced injury most commonly affects the Bundle of His and left bundle branch. We documented 15.5% of our cohort had a baseline RBBB, higher than in most contemporary studies, which may have also influenced our high incidence of PPMI. Results from the STS/ACC registry recorded a baseline RBBB rate of 10.3%(185), whilst the PARTNER cohorts of balloon-expandable valves(45) and the 2023

OPTIMIZE PRO(186) study of self-expanding valves had rates of 8.1% and 6.9% respectively. In baseline RBBB, PPMI has been reported in roughly 50% of cases regardless of valve type(187), and we noted a similar rate. Prophylactic PPMI prior to TAVI in patients with baseline RBBB may shorten length of stay, decrease procedural duration, and lower cardiovascular readmission(164, 188) . With prospective validation, this may represent a safe approach for incorporating patients with baseline RBBB into expedited discharge protocols.

Incorporating RAP to induce AV Wenckebach at rates between 70 to 120 bpm to specifically assess AV nodal conduction post-TAVI was first proposed by Krishnaswamy *et al.* (2019)*(69)*. Beyond validating their results, we demonstrate it can be performed *prior* to TAVI and serve as an independent predictor of PPMI, even after adjusting for other variables. A drawback of RAP is its futility in CHB or AF. On the other hand, the HV interval can be assessed in AF and is also less prone to vagal and medication influence. As a sensitive marker of infra-Hisian conduction, Rivard *et al.* (2015) published that ΔHV>13ms increased PPMI risk(68). We observed statistical significance at a lower threshold (ΔH >10ms) and combined it with peri-procedural CHB where it was assumed the HV interval was prolonged to the point of being absent.

The CONDUCT-TAVI Score combines the three independent factors (baseline RBBB, ΔHV>10ms (or CHB), or pre-TAVI RAP induced AV Wenckebach) and demonstrated strong predictive accuracy (AUC 0.794) with a linear correlation to PPMI risk (Figure 3). Notably, a score of 0, observed in 38% of the cohort, had a negative predictive value of 98%, which may aid implanters in identifying low-risk patients suitable for rapid discharge. Given that this score necessitates the measurement of the HV interval and rapid atrial pacing, it may initially seem

limited to centres equipped to incorporate EP studies into their TAVI procedures. However, our study demonstrates that mobile EP systems provide an accessible and cost-effective alternative.

Self-expanding valves historically have had comparatively higher PPMI incidence, attributed to greater oversizing, radial force, and typically a deeper implant. However, redistribution of radial force along with the introduction of the *cusp-overlap* deployment technique(186) have reportedly reduced PPMI rates. Cusp-overlap isolates the non-coronary cusp during deployment, thereby elongating the LVOT to achieve a precise high implant, which may explain why self-expanding valves did not *independently* predict PPMI on our multivariable analyses. Similarly, factors such as oversizing, membranous septum length, and implantation depth, which are believed to amplify the interaction between the prosthesis and conduction system, did not remain significant predictors on multivariable analyses.

There was no association found between calcium volume and distribution with PPMI, aligning with a recent meta-analysis(189), which may be due to conflicting mechanisms of His Bundle injury: via direct infiltration or asymmetric valve expansion, driven by opposing calcium distribution. Similarly, we did not find any association between annular ellipticity and conduction, which has also been proposed previously(190).

The comprehensive evaluation of late PPMI post-TAVI constitutes a notable strength of this study, particularly given heterogeneous prior results(173). Late PPMI occurred in 7.5%, with half occurring in the first month, followed by a tapering yet persistent risk up to one year (Figure 2). The recently published D-PACE(191) scoring system for delayed PPMI identified self-expanding

valves, implantation depth, baseline RBBB, new bundle branch block, and PR prolongation as independent predictors in a primarily retrospective cohort. However, it did not include anatomical and EPS-derived parameters, which we have shown to be significant contributors(191). Our sub-analyses (Supplementary Table 3) suggest that early PPMI was driven more by procedural factors (valve type, membranous septum, and oversizing), whereas late PPMI correlated with markers of impaired baseline infra-Hisian conduction, which may serve as directions for future research.

New-onset atrial fibrillation

Without continuous rhythm monitoring, major contemporary randomised trials have reported NOAF incidence between 7.0-9.8% at 1-year(138, 158), whilst a recently published study used Holter monitoring to report an incidence of 7.0% at *14 days* post-TAVI(74). This is the first study to use ILRs to document the incidence of NOAF at 1-year after TAVI is 21.7%. The specific role of TAVI in triggering AF remains uncertain, as both age and AS related myocardial fibrosis, diastolic impairment and atrial enlargement predispose to AF. Prior work in heart failure patients reported subclinical device-detected AF in 23% at four-years(192). We observed 46.5% patients either had a previous history of AF or developed NOAF within 1-year post-TAVI. Whether our findings merely indicate a heightened incidence of device-detected AF within the high-risk AS population, or whether electrical and anatomical remodelling post-TAVI directly contributes, could be a direction of future work.

However, the management implications of device-detected NOAF remain unclear. The LOOP study(193) which randomised patients with cryptogenic stroke to ILRs, reported increased AF

detection and anticoagulation, but without a reduction in stroke risk(193). Contrastingly, a 2015 study monitored patients for 24 hours prior to their TAVI, detecting NOAF in 6.4%, which was associated with a 7-fold increase in 30-day stroke risk. Among the 13 patients in our cohort with ischemic stroke or TIA, 5 had known AF, while 3 were identified with NOAF. The thromboembolic risk may differ in TAVI populations, and prior studies conducted in stroke cohorts may not be generalisable. Currently, major European and American guidelines continue to recommend anticoagulation for patients with a high thromboembolic risk and device-detected subclinical AF episodes lasting longer than 5 minutes.

Limitations

The non-blinded observational design of the study may have introduced potential bias. The primary outcome (PPMI due to HGAVB) was determined at the discretion of the implanter or treating cardiologist, rather than by the study protocol. Whilst the two most common valve systems were used, the results should not be generalised to other commercially available valve platforms. Furthermore, implantation depth was estimated based on fluoroscopic projections, and variability in two-cusp and three-cusp views may have introduced minor measurement inconsistencies. Finally, as an observational cohort design, the study used a sensitivity-based power calculation rather than being specifically designed for predictive modelling. Consequently, the CONDUCT-TAVI score, which was developed and evaluated within this population, would benefit from external validation to enhance the model's credibility.

6.6 Conclusions

This prospective study of 200 patients undergoing elective TAVI, combined with one year of continuous rhythm monitoring, suggests that the true incidence of HGAVB, new persistent LBBB and NOAF may be higher than previously recognised. Furthermore, after accounting for demographic, anatomic, electrophysiological and procedural factors, the key independent predictors of PPMI risk were found to be pre-existing right bundle branch block and impaired AV nodal and infra-Hisian conduction. These were used to develop the CONDUCT-TAVI Score, which demonstrated a negative predictive value of 98% within this cohort. Incorporating these findings into clinical practice can enable implanters to more effectively stratify patients for early discharge.

Funding: This is an investigator initiated and funded project. The implantable loop recorders were provided in kind by BIOTRONIK. Dr. Karan Rao is supported through a National Health and Medical Research Council and Heart Research Australia Postgraduate Scholarship.

Disclosures: The authors have no disclosures or conflicts of interest to report.

Supplemental Material:

- Supplementary Methods
- Supplementary Tables S1-S6
- Supplementary Figures 1-5

6.7 Tables and Figures

	No PPMI (n = 158)	**PPMI (n = 42)**	***p* value**
Demographics			
Age (years), median (IQR)	83.0(10.0)	81.0 (12.0)	0.823
Male, n (%)	98 (62.0)	32 (67.2)	0.070
BMI [kg/m^2], median (IQR)	27.4(7.5)	28.4(7.2)	0.085
STS score (%), median (IQR)	3.0(2.9)	1.6(2.5)	0.428
Hypertension, n (%)	127 (80.4)	36 (84.5)	0.508
Hyperlipidaemia, n (%)	64 (40.5)	26 (61.9)	0.860
Diabetes mellitus, n (%)	40 (25.3)	15 (35.7)	0.181
Coronary artery disease, n (%)	58 (36.7)	12 (28.6)	0.367
Prior percutaneous coronary intervention, n (%)	41 (25.9)	12 (28.6)	0.844
Prior coronary artery bypass grafting, n (%)	17 (10.8)	4 (9.5)	0.999
Peripheral arterial disease (PAD), n (%)	9 (5.7)	3 (7.1)	0.719
Prior atrial fibrillation, n (%)	48 (30.4)	14 (33.3)	0.711
Prior Stroke, n (%)	15 (9.5)	2 (4.8)	0.534
Chronic obstructive pulmonary disease (COPD), n (%)	16 (10.1)	5 (11.9)	0.778
Chronic kidney Disease (CKD), n (%)	43 (27.2)	13 (31.0)	0.700
Medications			
Beta-blocker, n (%)	60(38.0)	13 (30.1)	0.473
Ca-channel blocker, n (%) (non-dihydropyridine)	9 (5.7)	3 (7.1)	0.718
Digoxin, n (%)	9 (5.7)	2 (4.8)	0.99
Other Antiarrhythmic, n (%)	9 (5.7)	3 (7.1)	0.99
Anticoagulation, n (%)	32 (20.3)	9 (21.4)	0.833
Aspirin, n (%)	72 (45.6)	16 (38.1)	0.451
Bloods			
Haemoglobin (g/L), mean, SD	126.8±16.5	128.1±18.6	0.343
Creatinine (umol/L), median, (IQR)	89.5(36.5)	90.0(47.5)	0.119

eGFR (ml/min/1.73m2), median (IQR)	62.0(31.0)	67.0(30.5)	0.323
Echocardiography			
Mean gradient (mmHg), median, (IQR)	42.0(17.3)	43.0(14.0)	0.654
Aortic valve area (cm2), median, (IQR)	0.8(0.3)	0.8(0.3)	0.362
LVEF (%), median, IQR)	60.0(5.0)	60.0(7.5)	0.192
CT TAVI			
Bicuspid	11 (7.0)	3 (9.4)	0.679
MSL (mm) mean, SD	3.1±2.3	2.0±2.2	0.003
Annulus area (mm^2) median, (IQR)	466.1(114.1)	517.1(145.1)	0.099
Annulus perimeter (mm), mean (SD)	77.9±8.4	80.0±7.5	0.069
Ellipticity index, mean (SD)	0.2±0.06	0.2±0.06	0.466
Aortic take-off angle (degrees), median, IQR)	50.0(11.0)	50.0(13.0)	0.275
DLZ Calcium, mm^3, median (IQR)			
Total	705.0(222.0)	762.5(730.0)	0.862
NCC	279.0(300.0)	402.5(388.0)	0.224
RCC	185.0(255.0)	203.0(218.0)	0.602
LCC	188.0(222.0)	174.5(201.0)	0.285
LVOT Calcium mm^3, median (IQR)	9.0(58.0)	15.0(34.0)	0.309
Procedural			
Valve type, n (%)			**0.011**
Balloon-expandable	68 (43.0)	9 (21.4)	
Self-expandable	90 (57.0)	33 (78.6)	
Valve model, n (%)			0.063
S3	21 (13.3)	1 (2.4)	
S3 Ultra	47 (29.7)	8 (19.0.	
Evolut R	73 (46.2)	28 (66.7)	
Evolut Pro	8 (5.1)	1 (2.4)	
Evolut Pro Plus	4 (2.5)	3 (7.1)	
Evolut FX	5 (3.2)	1 (2.4)	
Valve size (mm), n (%)			**0.002**
20	3 (1.9)	1 (2.4)	
23	23 (14.6)	1 (2.4)	
26	57 (36.1)	8 (19.1)	
29	48 (30.4)	14 (33.3)	
34	27 (17.1)	18 (42.9)	
Annular oversizing (%), mean, SD	14.8±9.2	19.7±8.1	**<0.001**
	14.5±12.1	19.3±10.6	**0.007**

LVOT oversizing (%), mean, SD	77 (48.7)	10 (23.8)	**0.005**
TAVI guidewire, n (%)	81 (51.3)	32 (76.2)	
Safari	27 (17.1)	10 (23.8)	0.267
Lunderquist	6 (3.8)	1 (2.4)	0.657
Pre-dilatation, n (%)	3.54±1.95	3.77±2.14	0.267
Post-dilatation, n (%)			
Implant depth (mm), mean, SD			
MSL-ID (mm), mean, SD	-0.45±2.88	-1.84±3.1	**0.005**
Transient CHB in TAVI, n (%)	17 (10.8)	23 (54.8)	**<0.001**
Length of stay (days)			
Median (IQR)	3.0(1.0)	3.0(4.0)	0.400

Table 1: Baseline demographics, medications, bloods, imaging and procedural results. SD: standard deviation; IQR: interquartile range; BMI: body mass index; STS: Society of Thoracic Surgeons; LVEF: left ventricular ejection fraction; MSL: membranous septum length; DLZ: device landing zone; NCC: non-coronary cusp; RCC: right coronary cusp; LCC: left coronary cusp; LVOT: left ventricular outflow tract; MSL-ID: membranous septum length – implant depth; CHB: complete heart block

	No PPMI (n=158)	PPMI (n=42)	P value
12-lead ECG			
Baseline ECG			
Heart rate (ms), mean	71.6±12.7	69.6±12.3	0.184
Rhythm, n (%)			0.305
Sinus rhythm	89 (56.3)	25 (59.5)	
First-degree AVB	42 (26.6)	7 (16.7)	
High-degree AVB	0 (0.0)	0 (0.0)	
AF or flutter	27 (16.1)	10 (23.8)	
PR (ms), median (IQR)	180.0(47.0)	180.0(45.5)	0.870
QRS (ms), median (IQR)	88.0(24.0)	108.0(63.0)	**<0.001**
LBBB, n (%)	9 (5.7)	3 (7.1)	0.718
RBBB, n (%)	14 (8.8)	17 (40.5)	**<0.001**
Immediately post TAVI			
Heart rate (ms), median (IQR)	78.0(19.5)	75.0(16.5)	**<0.001** **<0.001**
Rhythm, n (%)	61 (38.6)	6 (14.3)	
Sinus rhythm	59 (37.3)	10 (23.8)	
First-degree AVB	5 (3.1)	19 (45.2)	
High-degree AVB	30 (19.0)	5 (11.9)	
AF or flutter	3 (1.9)	2 (4.8)	
Other	196.0(52.0)	208.0(34.0)	0.228
PR (ms), median (IQR)	132.0(42.0)	152.0(26.0)	**<0.001**
QRS (ms), median (IQR)	82 (52.9)	12 (44.0)	**0.005**
LBBB, n (%)	16 (10.3)	10 (37.0)	**0.035**
RBBB, n (%)			
4-hour post TAVI	74.0(18.0)	68.0(21.0)	**0.024**
Heart rate (ms), median (IQR)	72 (45.9)	11 (26.2)	**<0.001**
Rhythm, n (%)	53 (33.8)	9 (21.4)	
Sinus rhythm	2 (1.3)	15 (35.7)	
First-degree AVB	29 (18.5)	5 (11.9)	
High-degree AVB	190.2±32.7	207.8±40.5	**0.016**
AF or flutter	112.0(45.0)	152.0(34.0)	**<0.001**
PR (ms), mean, SD	53 (34.2)	11 (39.3)	0.237
QRS (ms), median (IQR)	14 (9.0)	11 (39.1)	**0.007**
LBBB, n (%)	0 (0.0)	0 (0.0)	
RBBB, n (%)			
Other	70.0(16.5)	68.0(25.0)	0.033
24-hour post TAVI			**<0.001**
Heart rate (ms), median (IQR)	83 (52.5)	9 (21.4)	
Rhythm	46 (29.1)	8 (19.0)	
	1 (0.6)	20 (47.7)	

Sinus rhythm	28 (17.7)	5 (11.9)	
First-degree AVB	186.0(43.0)	194.0(81.0)	0.171
High-degree AVB	101.0(44.0)	150.0(54.0)	**<0.001**
AF or flutter	38 (24.2)	10 (38.5)	0.576
PR (ms), median (IQR)	15 (9.5)	9 (21.4)	0.057
QRS (ms), median (IQR)			
LBBB, n (%)			
RBBB, n (%)			
Electrophysiology study			
Pre-TAVI			
AH (ms), median (IQR)	104.0(45.0)	108.5(53.5)	0.345
HV (ms), median (IQR)	56.0(13.5)	59.0(17.5)	0.407
RAP performed, n (%)	129 (81.6)	32 (76.2)	0.511
Inducible AVW, n (%)	28 (21.9)	18 (56.3)	**<0.001**
Post-TAVI			
AH (ms), median (IQR)	108.0(59.5)	109.5(59.5)	0.364
HV (ms), median (IQR)	66.0(16.0)	77.0(34.0)	0.075
RAP performed, n (%)	120 (75.9)	17 (41.5)	**<0.001**
Inducible AVW, n (%)	29 (24.2)	11 (64.7)	**0.001**
ΔAH (ms), median (IQR)	4.0(18.0)	6.0(36.3)	0.281
ΔHV (ms), median (IQR)	6.0(12.0)	14.0(19.5)	**0.005**

Table 2: Pre- and post-TAVI electrophysiology characteristics. AV: atrioventricular; LBBB: left bundle branch block; RBBB: right bundle branch block; AF: atrial fibrillation; AH: Atrial-His interval; HV: His-Ventricle interval; AVW: AV Wenckebach

Clinical outcomes	Overall (n = 200)
PPMI	48 (24.0)
PPMI secondary to HGAVB, n (%)	**42 (21.0)**
PPMI secondary to early HGAVB (<48 hours)	27 (13.5)
PPMI secondary to late HGAVB (>48 hours – 1 year)	15 (7.5)
PPMI secondary to tachy-brady syndrome or sick-sinus syndrome	6 (3.0)
Time to pacemaker (days), median	1.5 (±16.0)
Time to delayed (>48 hours) pacemaker (days), median	37.0 (± 87.0)
New onset LBBB	
New LBBB immediately post TAVI, n (%)	82/188 (43.6)
New LBBB at 4 hours, n (%)	52/188 (27.7)
New LBBB at 24 hours (persistent), n (%)	36/188 (19.1)
New LBBB at 1 month (permanent), n (%)	39/188 (20.7)
Tachyarrhythmia (1 year)	
NOAF, n (%)	30/138 (21.7)
Time to NOAF (days), median	20.5 (68.0)
Ventricular tachycardia or fibrillation, n (%)	1 (0.5)
Clinical outcomes (1 year)	
All-cause mortality, n (%)	15 (7.5)
Cardiovascular mortality, n (%)	5 (2.5)
Any rehospitalisation, n (%)	60 (30.0)
Cardiovascular rehospitalisation, n (%)	34 (17.0)
Major vascular complication or bleeding, n (%)	8 (4.0)
Stroke or TIA, n (%)	13 (6.5)
Endocarditis, n (%)	3 (1.5)

Table 3: Primary outcome and clinical outcomes. PPMI: permanent pacemaker implantation, HGAVB: high-grade atrioventricular block; LBBB: left bundle branch block; NOAF: new onset atrial fibrillation; TAVI: transcatheter aortic valve implantation

Patient	Time from TAVI to NOAF (days)	AF status at completed follow up	AF burden (average % of day)	Total AF episodes (to completed follow up*)	Anticoagulation commenced
1	14	Paroxysmal	<0.1	3	Yes
2	13	Paroxysmal	13.7	304	Yes
3	4	Paroxysmal	<0.1	3	Yes
4	24	Paroxysmal	0.1	47	Yes
5	1	Paroxysmal	0.3	2244	Yes
6	0	Paroxysmal	2.3	86	Yes
7	93	Paroxysmal	<0.1	4	Yes
8	4	Paroxysmal	1.3	19	Yes
9	80	Paroxysmal	1.0	43	Yes
10	0	Paroxysmal	15.4	11	Yes
11	154	Paroxysmal	<0.1	1	No
12	20	Paroxysmal	<0.1	3	Yes
13	25	Paroxysmal	21.1	1968	Yes
14	6	Paroxysmal	<0.1	35	Yes
15	253	Paroxysmal	<0.1	3	Yes
16	22	Persistent	100	n/a	Yes
17	7	Paroxysmal	38.7	87	Yes
18	33	Paroxysmal	1.0	256	Yes
19	223	Paroxysmal	<0.1	8	Yes
20	15	Paroxysmal	<0.1	4	Yes
21	21	Paroxysmal	33.4	693	Yes
22	3	Persistent	100	n/a	Yes
23	57	Persistent	100	n/a	Yes
24	294	Paroxysmal	<0.1	3	Yes
25	14	Paroxysmal	1.0	33	Yes
26	7	Paroxysmal	6.1	615	Yes
27	267	Paroxysmal	2.5	98	Yes
28	0	Persistent	100	n/a	Yes
29	93	Paroxysmal	0.6	5	No
30	42	Paroxysmal	6.9	133	Yes

Table 4: Patients with NOAF (n=30) and description of characteristics, including time to NOAF, AF status at completion of follow up, average daily AF burden (%), and total AF episodes across period of

follow up (derived from implantable loop recorder data), and whether anticoagulation was commenced due to the diagnosis of NOAF. TAVI: transcatheter aortic valve implantation); NOAF: new onset atrial fibrillation

	Univariable, OR (95% CI)	**P value**	**Multivariable, OR (95% CI)**	**P value**
Age	1.01 (0.96-1.07)	0.624		
Gender	0.51 (0.23-1.11)	**0.091**	1.29 (0.44-3.80)	0.648
BMI	1.05 (0.98-1.12)	0.145		
STS Score	0.94 (0.80-1.11)	0.475		
MSL (mm)	0.80 (0.67-0.94)	**0.008**		
Annular Ellipticity	0.70 (0.01-214.3)	0.901		
Total DLZ Calcium Volume	1.00 (1.00-1.01)	0.327		
NCC LVOT Calcium volume	1.01 (1.0-1.01)	0.379		
Pre-TAVI PR	1.00 (0.99-1.01)	0.574		
ΔPR (pre / post TAVI)	1.03 (1.01-1.05)	**0.013**		
RBBB	6.99 (3.07-15.96)	**<0.001**	**5.45 (1.67-17.84) β: 1.696**	**0.005**
LBBB	1.27 (0.33-4.92)	0.726		
Pre-existing AF	1.15 (0.56-2.37)	0.713		
Pre-TAVI HV Interval	1.02 (0.99-1.05)	0.241		
Post-TAVI HV Interval	1.04 (1.01-1.08)	**0.015**		
ΔHV >10 (or CHB)	5.11 (2.29-11.40)	**<0.001**	**3.62 (1.23-10.67) β: 1.308**	**0.020**
AVW Pre	4.59 (2.03-10.37)	**<0.001**	**3.70 (1.37-9.98) β: 1.287**	**0.010**
AVW Post	5.75 (1.96-16.92)	**0.001**		
Self-expanding valve	2.77 (1.24-6.18)	**0.013**	2.05 (0.40-10.66)	0.392
Annular Oversizing %	1.07 (1.03-1.12)	**0.002**	1.03 (0.95-1.13)	0.481
LVOT Oversizing %	1.04 (1.01-1.07)	**0.025**		
Implant depth	1.06 (0.89-1.27)	0.508		
Implant depth – MSL	0.85 (0.75-0.97)	**0.013**	0.85 (0.71-1.01)	0.070
Pre or post dilatation	1.28 (0.57-2.88)	0.551		
New persistent LBBB (24 hours)	0.71 (0.28-1.84)	0.482		

Table 5: Logistic regression of pre-specified variables to predict new PPMI after TAVI. BMI: body mass index; STS: Society of Thoracic Surgeons Risk Score; MSL: membranous septum length; LVOT: left ventricular outflow tract; DLZ: device landing zone; NCC: non-coronary cusp; RBBB: right bundle branch block; LBBB: left bundle branch block; AF: atrial fibrillation; HV: His-Ventricle Interval; CHB: complete heart block; AVW: Atrioventricular Wenckebach; β: beta coefficient

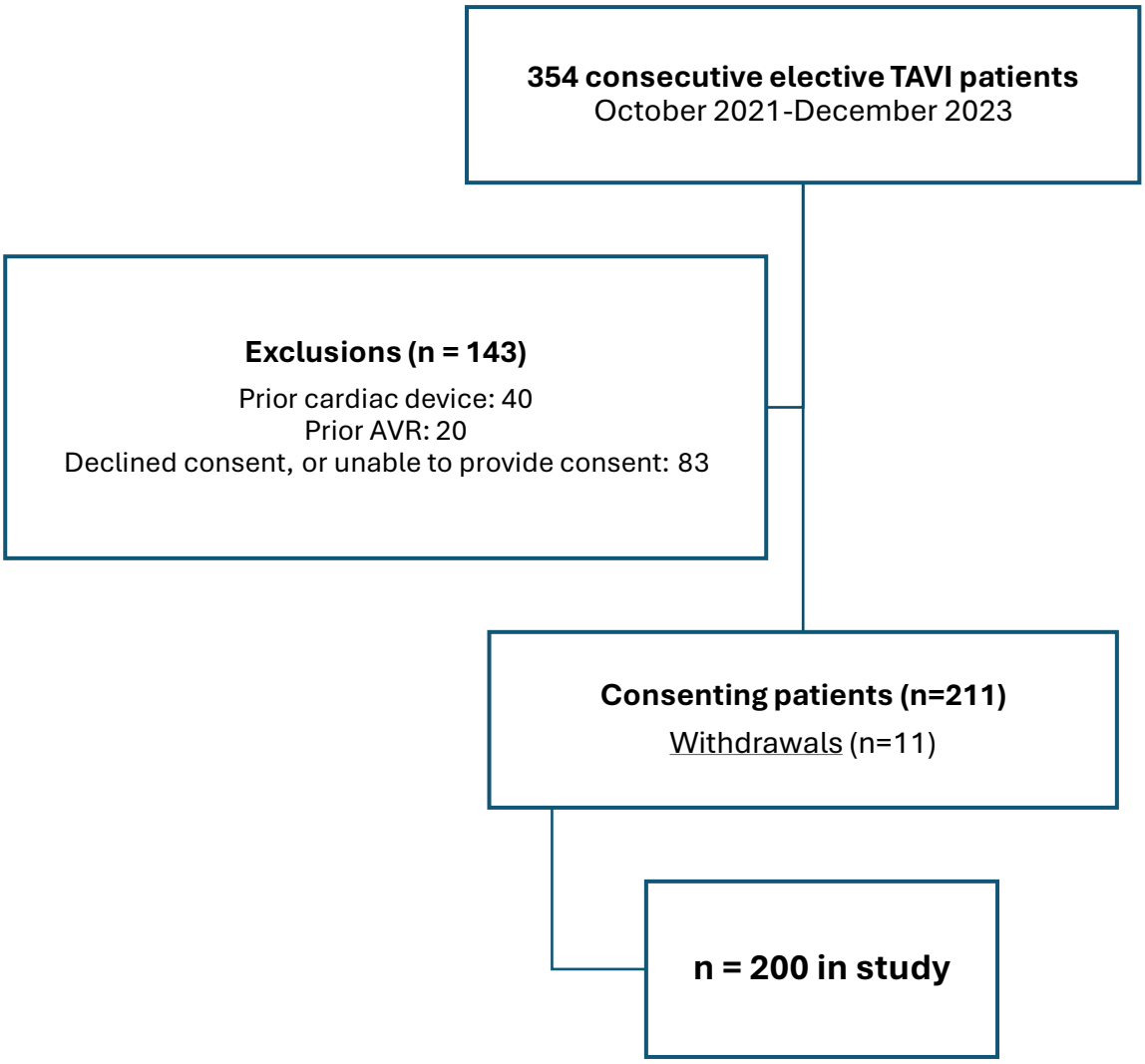


Figure 1: CONDUCT-TAVI Study Pathway

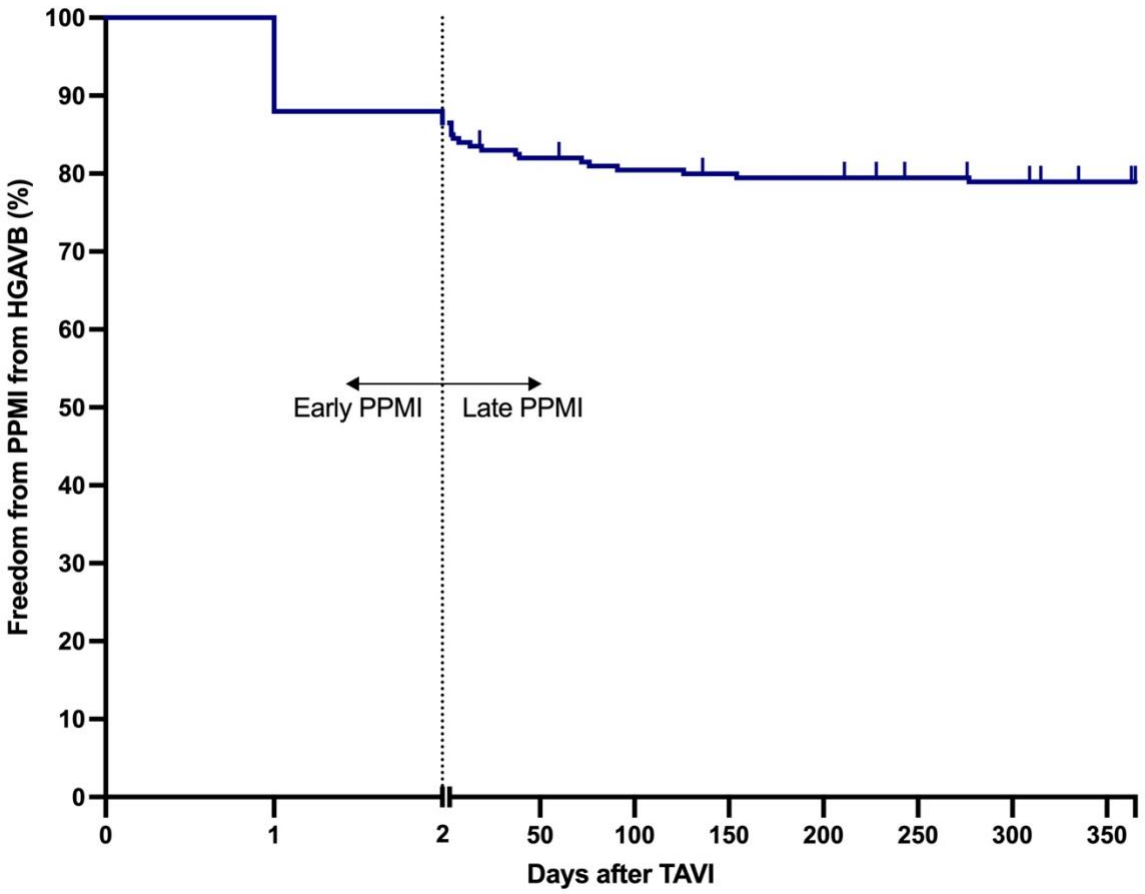


Figure 2: Freedom from PPMI from HGAVB at 1 year after TAVI. PPMI: permanent pacemaker implantation; HGAVB: high-grade atrioventricular block.

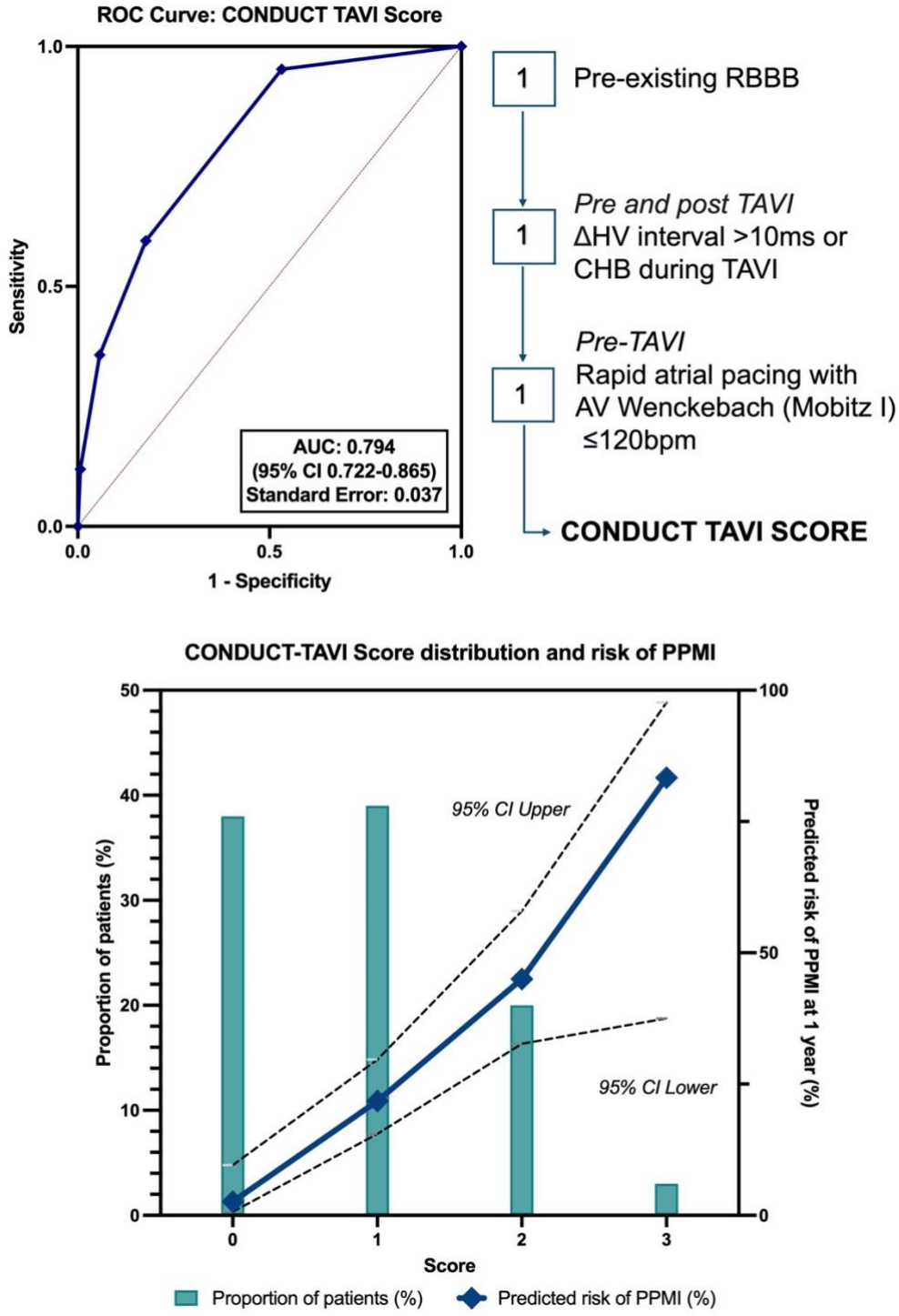
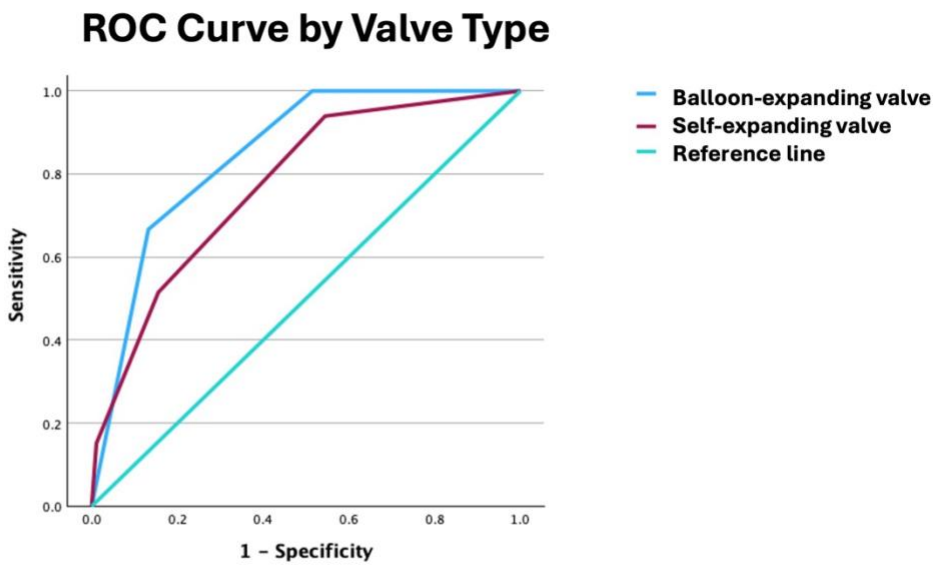


Figure 3: Receiver operator characteristic (ROC) Curve CONDUCT-TAVI Score (top); CONDUCT-TAVI Score distribution across cohort (bar graph, left axis), and respective predicted risk of PPMI at 1 year (line graph, right axis) with 95% Confidence Intervals (dotted line). AUC: area under the curve; CI: confidence interval; RBBB: right bundle branch block; HV: His-Ventricle; CHB: complete heart block.



Area Under the ROC Curve					
Test Result Variable(s): CONDUCT-TAVI Score					
	Area under the curve (AUC)	Standard error	Asymptotic Significance	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Self-expanding valves	0.774	0.046	0.000	0.684	0.863
Balloon-expandable valves	0.848	0.056	0.000	0.739	0.957
Comparison of AUC	Z = -1.021, p = 0.307 (using Hanley & McNeil method for comparing AUC from independent samples)				

CONDUCT-TAVI PPM SCORE of 0	**All valves (n=200)**	**Balloon expanding (n=77)**	**Self-expanding (n=123)**
Statistic	Value (95% CI)	Value (95% CI)	Value (95% CI)
Sensitivity (%)	95.2 (83.8-99.4)	100.0 (66.4-100.0)	93.9 (79.8 – 99.3)
Specificity (%)	46.8 (38.9-54.9)	48.5 (36.2-61.0)	45.6 (35.0-56.4)
Disease prevalence (%)	21.0	11.7	26.8
Positive Predictive Value (%)	32.3 (28.8-35.9)	20.5% (17.0-24.5)	38.7 (33.9-43.8)
Negative Predictive Value (%)	97.6 (90.5-99.3)	100.0 (89.4-100.0)	95.4 (84.0-98.8)

Figure 4: Performance of the CONDUCT-TAVI score when arranged by valve type.

6.8 Supplementary Materials

Contents:

- Methods
- Supplementary Tables (Tables S1-S6)
- Supplementary Figures 1-5

Supplementary Methods

Sample Size Calculation

- The sample size was calculated using the Wilson Interval for calculating a two-sided 95% confidence interval with a width equal to 0.15. The one-sample sensitivity was estimated at 0.98, and the prevalence of our primary outcome was estimated at 0.15 (Wilson Score Interval). Using these calculations, it was estimated that a sample size of 194 would be required, and assuming a drop-out rate of 5%, a total enrolment sample size of 205 was estimated.
- The calculation below was completed with a local university biostatistician and was performed on PASS (Power Analysis and Sample Size Software) Version 20.0.3 (2020)

Numeric Results for Two-Sided Confidence Intervals for One-Sample Sensitivity
Confidence Interval Formula: Score (Wilson)

Confidence Level	Sample Size (N)	Target Width	Actual Width	Sensitivity	Lower Limit	Upper Limit	Prevalence	Number of Positives
0.95263	194	0.15	0.15	0.98	0.84769	0.99769	0.15	29

Schedule	Admission for TAVI	Post-TAVI Visits (28 days, 6 months and 12 months after TAVI)
Informed Consent	✓	
Inclusion / Exclusion criteria	✓	
Demographics	✓	
Medical History	✓	✓
Medications List	✓	✓
Height, Weight, Vital Signs	✓	
Electrocardiogram	✓	✓
Transthoracic Echocardiogram	✓	✓ (28 days and 12 months only)
Rapid Atrial Pacing	✓	
Measurement of AH, HV Interval	✓	
Loop recorder implantation	✓	
Loop recorder or pacemaker interrogation		✓
Adverse Event & Serious Adverse Event Assessment	✓	✓

Supplementary Table S1: CONDUCT TAVI Patient schedule; TAVI: transcatheter aortic valve implantation; AH: atrial-His; HV: His-Ventricle

Patient ID	Days from TAVI to PPM	Indication	Long-term pacing %	
			AP (%)	VP (%)
1	1	Early HGAVB	0	1
46	1	Early HGAVB	3	5
47	1	Early HGAVB	n/a	12
51	0	Early HGAVB	8	64
56	1	Early HGAVB	89	0
58	1	Early HGAVB	16	87
59	39	Asymptomatic CHB (TAVI Endocarditis)	21	100
60	76	Symptomatic CHB	22	100
64	72	Asymptomatic HGAVB	38	76
68	37	Symptomatic transient CHB	n/a	100
71	202	Sick sinus syndrome / tachycardia bradycardia syndrome	n/a	22
78	0	Early HGAVB	n/a	100
79	1	Early HGAVB	n/a	100
80	1	Early HGAVB	45	57
83	13	Asymptomatic transient HGAVB	58	1
86	6	Sick sinus syndrome / tachycardia bradycardia syndrome	34	1
93	4	Symptomatic transient CHB	38	6
97	0	Early HGAVB	n/a	100
104	7	Asymptomatic transient HGAVB	20	76
109	3	Asymptomatic HGAVB	19	2
110	91	Symptomatic transient CHB	81	1
116	0	Early HGAVB	n/a	80
120	19	Asymptomatic transient CHB	1	1
121	0	Early HGAVB	n/a	85
129	10	Sick sinus syndrome / tachycardia bradycardia syndrome	1	78
134	13	Sick sinus syndrome / tachycardia bradycardia syndrome	1	65
142	1	Early HGAVB	1	51
147	154	Symptomatic transient CHB	1	1
150	1	Early HGAVB	1	96
152	0	Early HGAVB	88	5

153	2	Early HGAVB	Died in hospital	
154	0	Early HGAVB	0	100
158	126	Transient symptomatic CHB	35	84
165	0	Early HGAVB	Did not have PPM check performed	
167	1	Early HGAVB	55	100
169	3	Transient symptomatic CHB	n/a	98
171	1	Early HGAVB	1	32
177	0	Early HGAVB	6	1
178	3	Symptomatic transient CHB	3	85
179	252	Sick sinus syndrome / tachycardia bradycardia syndrome	n/a	
180	0	Early HGAVB	7	8
182	2	Early HGAVB	8	44
188	277	Asymptomatic transient CHB	10	60
194	0	Early HGAVB	Did not have PPM check performed.	
200	0	Early HGAVB	n/a	25
202	0	Early HGAVB	64	1
204	347	Sick sinus syndrome / tachycardia bradycardia syndrome	51	99

Supplementary Table S2: Pacing indication and extended pacing requirement for all patients that underwent a permanent pacemaker implantation during the study. AP: atrial pacing; VP: ventricular pacing.

*Note: 211 patients were recruited and 11 withdrew.

Collinear Variables deemed significant on univariable logistic regression	**Variable selected**	**Rationale**
ΔPR (pre/post TAVI) Post-TAVI HV Interval ΔHV >10 (or CHB)	ΔHV >10 (or CHB)	On univariable analysis, ΔHV >10 (or CHB) demonstrated the strongest association with the outcome (OR 5.11, 95% CI 2.29–11.40, p < 0.001), compared to ΔPR (pre/post-TAVI) (OR 1.03, 95% CI 1.01–1.05, p = 0.013) and the post-TAVI HV interval alone (OR 1.04, 95% CI 1.01–1.08, p = 0.015). Given the substantially

		greater effect size and statistical significance, ΔHV >10 (or CHB) was selected for inclusion in the multivariable model.
AV Wenckebach (pre-TAVI) AV Wenckebach (post-TAVI)	AV Wenckebach (pre-TAVI)	Although post-TAVI AV Wenckebach had a slightly larger effect size (OR 5.75 vs. 4.59), its confidence interval was broader (2.29–11.40 vs. 2.03–10.37) and p-values were comparable ($p = 0.001$ vs. $p < 0.001$). Due to uncertainty, a likelihood ratio was performed which favoured post-TAVI AV Wenckebach; however, we prioritized pre-TAVI AV Wenckebach for model inclusion due to its greater clinical utility. Post-TAVI AV Wenckebach cannot be reliably assessed in patients who develop high-grade AV block or atrial fibrillation post-procedure, and relying on it would reduce the generalizability of the model.
Implant depth-MSL MSL (alone)	Implant depth-MSL	Implant depth-MSL and MSL alone had similar effect sizes on univariable analysis (OR 0.85 vs. 0.80) with comparable confidence interval widths (0.75–0.97 vs. 0.67–0.95). However, a likelihood ratio of 1224.5 strongly favoured the combined Implant Depth-MSL variable, supporting its selection for multivariable modelling.
Annular oversizing (%) LVOT oversizing (%)	Annular oversizing (%)	Both annular and LVOT oversizing (%) had similar effect sizes (OR 1.07 vs. 1.04) and confidence intervals on univariable analysis. A likelihood ratio of 1.62 marginally favoured annular oversizing %, which was therefore chosen for inclusion in the final model.

Supplementary Table S3: Rationale and detailed explanation for how collinearity was managed in Table 5: Logistic regression of pre-specified variables to predict new PPMI after TAVI) which was used for model creation (CONDUCT-TAVI Score).

	Univariable, HR (95% CI)	P value	Multivariable, HR (95% CI)	P value
Age	1.01(0.97-1.06)	0.592		
Gender	0.55(0.27-1.12)	0.097*	1.13(0.40-14.12)	0.824
BMI	1.04(0.99-1.10)	0.157		
STS Score	0.95(0.82-1.10)	0.506		
MSL (mm)	0.83(0.72-0.95)	**0.008***		
Annular Ellipticity	0.87(0.01-133.3)	0.957		
Total DLZ Calcium Volume	1.00(1.00-1.01)	0.310		
NCC LVOT Calcium volume	1.00(1.00-1.01)	0.187		
Pre-TAVI PR	0.99(0.99-1.01)	0.518		
ΔPR (pre / post TAVI)	1.02(1.01-1.04)	**0.007***		
RBBB	4.52(2.43-8.39)	**<0.001***	**4.35(1.23-14.12)**	**0.014**
LBBB	1.17(0.36-3.79)	0.791		
Pre-existing AF	1.12(0.59-2.14)	0.721		
Pre-TAVI HV Interval	1.02(0.99-1.05)	0.229		
Post-TAVI HV Interval	1.04(1.01-1.07)	**0.010***		
ΔHV >10 (or CHB)[1]	4.33(2.07-9.06)	**<0.001***	2.04(0.70-5.94)	0.192
AVW Pre	3.63(1.81-7.31)	**<0.001***	**4.51(1.57-12.96)**	**0.005**
AVW Post	5.06(1.87-13.70)	**0.001***		
Self-expanding valve	2.52(1.20-5.27)	**0.014***	0.74(0.15-3.66)	0.707
Annular Oversizing %	1.06(1.02-1.10)	**<0.001***	1.05(0.96-1.16)	0.300
LVOT Oversizing %	2.90(1.09-7.73)	**0.033***		
Implant depth	1.06(0.90-1.24)	0.477		
Implant depth – MSL	0.87(0.78-0.97)	**0.011***	0.73(0.61-0.88)	<0.001
Pre or post dilatation	1.31(0.64-2.66)	0.460		
New persistent LBBB (24 hours)	0.96 (0.47-1.95)	0.910		

Supplementary Table S4: Univariable and multivariable Cox-Regression analyses to assess hazard ratio of new PPMI secondary to HGAVB after TAVI. For collinear variables, a single variable was chosen based on statistical and clinical relevance (see Supplementary Table 3).

Secondary outcome						
Variable	**Early PPMI (27/200) OR (95% CI)**	**P value**	**Late PPMI (15/173) OR (95% CI)**	**P value**	**Persistent LBBB OR (95% CI)**	**P value**
Age	1.04 (0.97-1.11)	0.262	0.98 (0.90-1.06)	0.557	0.98 (0.93-1.04)	0.448
Gender	0.49 (0.19-1.27)	0.141	0.59 (0.18-1.95)	0.390	1.63 (0.78-3.39)	0.192
BMI	1.05 (0.97-1.13)	0.239	1.04 (0.950-1.14)	0.379	1.05 (0.99-1.13)	0.114
STS Score	1.02 (0.85-1.22)	0.842	0.80 (0.58-1.12)	0.194	0.91 (0.76-1.09)	0.302
Anti-arrhythmic	0.70 (0.29-1.67)	0.427	0.82 (0.27-2.50)	0.723	0.72 (0.33-1.57)	0.415
MSL (mm)	0.76 (0.62-0.93)	**0.009***	0.88 (0.69-1.12)	0.302	0.85 (0.71-1.01)	0.070
Total DLZ Calcium Volume	1.00 (1.00-1.01)	0.286	1.00 (0.99-1.01)	0.796	1.00 (0.99-1.01)	0.751
NCC LVOT Calcium volume	1.01 (0.99-1.01)	0.354	1.00 (0.99-1.00)	0.348	0.99 (0.99-1.01)	0.573
Δ PR (pre / post TAVI)	1.03 (1.01-1.06)	**0.032***	1.02 (0.99-1.05)	0.123	1.02 (1.00-1.04)	**0.049***
RBBB	4.23 (1.72-10.52)	**0.002***	9.00 (2.84-28.52)	**<0.001**	n/a	n/a
LBBB	0.56 (0.07-0.59)	0.594	2.54 (0.48-13.05)	0.262	n/a	n/a
Pre-existing AF	1.34 (0.59-3.19)	0.467	0.83 (0.25-2.75)	0.765	1.33 (0.62-2.83)	0.465
Pre HV	1.01 (0.97-1.05)	0.651	1.03 (0.98-1.08)	0.201	1.00 (0.97-1.04)	0.940
Post HV	1.01 (0.96-1.06)	0.838	1.06 (1.02-1.11)	**0.004**	1.01 (0.99-1.04)	0.347
Δ HV	1.05 (0.99-1.12)	0.113	1.08 (1.02-1.14)	**0.004**	1.04 (0.99-1.08)	0.068
CHB during deployment	24.02 (8.75-66.06)	**<0.001**	2.82 (0.81-9.82)	0.102	1.05 (0.44-2.51)	0.907
Δ HV >10 (or CHB)	7.34 (2.43-22.12)	**<0.001**	2.79 (0.91-20.85)	0.073	1.35 (0.65-2.78)	0.423

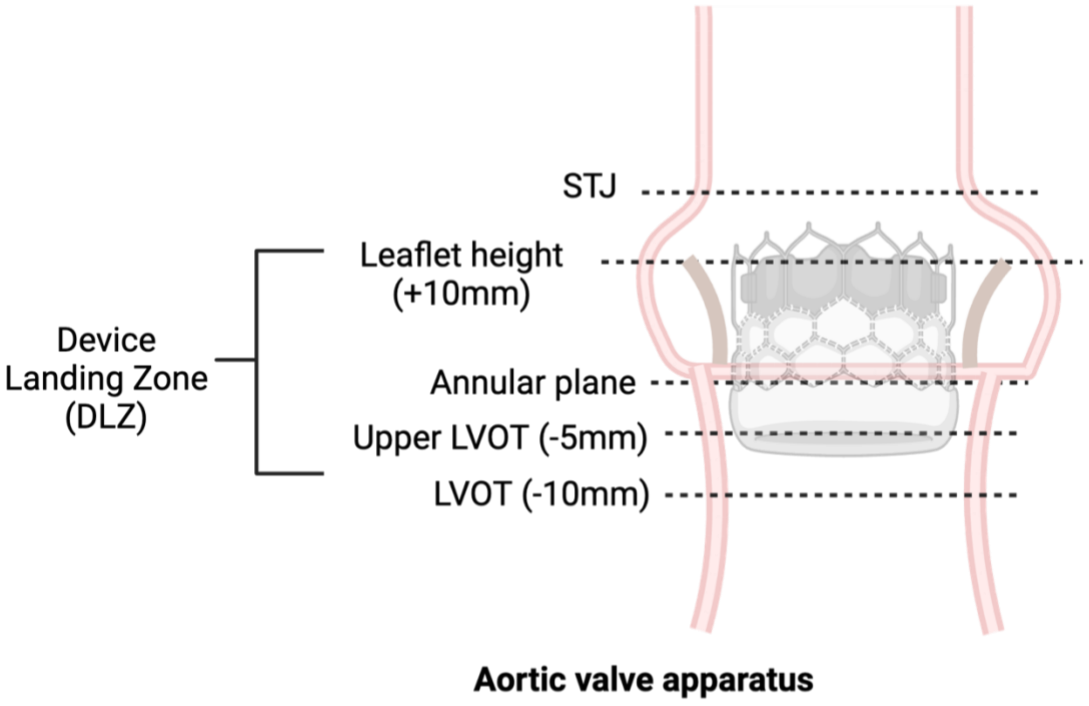
AVW Pre TAVI	4.67 (1.76-12.39)	**0.002***	3.57 (1.07-11.94)	**0.039**	2.01 (0.87-4.65)	0.101
AVW Post TAVI	16.94 (1.97-145.85)	**0.010**	3.14 (0.85-11.61)	0.087	1.57 (0.65-3.81)	0.320
Self-expanding valve	5.98 (1.74-20.61)	**0.005***	1.13 (0.39-3.34)	0.820	1.31 (0.61-2.81)	0.483
Annular oversizing %	1.10 (1.04-1.16)	**<0.001***	1.03 (0.97-1.09)	0.380	1.02 (0.98-1.07)	0.281
LVOT oversizing	1.06 (1.02-1.10)	**0.005**	0.99 (0.95-1.04)	0.820	1.02 (0.98-1.05)	0.348
Implant depth	1.05 (0.85-1.23)	0.632	1.07 (0.81-1.42)	0.639	1.51 (1.23-1.86)	**<0.001***
Implant depth – MSL	0.84 (0.72-0.97)	**0.017**	0.90 (0.74-1.09)	0.271	0.76 (0.66-0.89)	**<0.001***
Pre or post dilatation	2.20 (0.91-5.35)	0.081	0.29 (0.04-2.31)	0.244	0.92 (0.37-2.29)	0.862

Supplementary Table S5: Univariable logistic regression for the following secondary outcomes: early PPMI; late PPMI; and new-persistent LBBB.

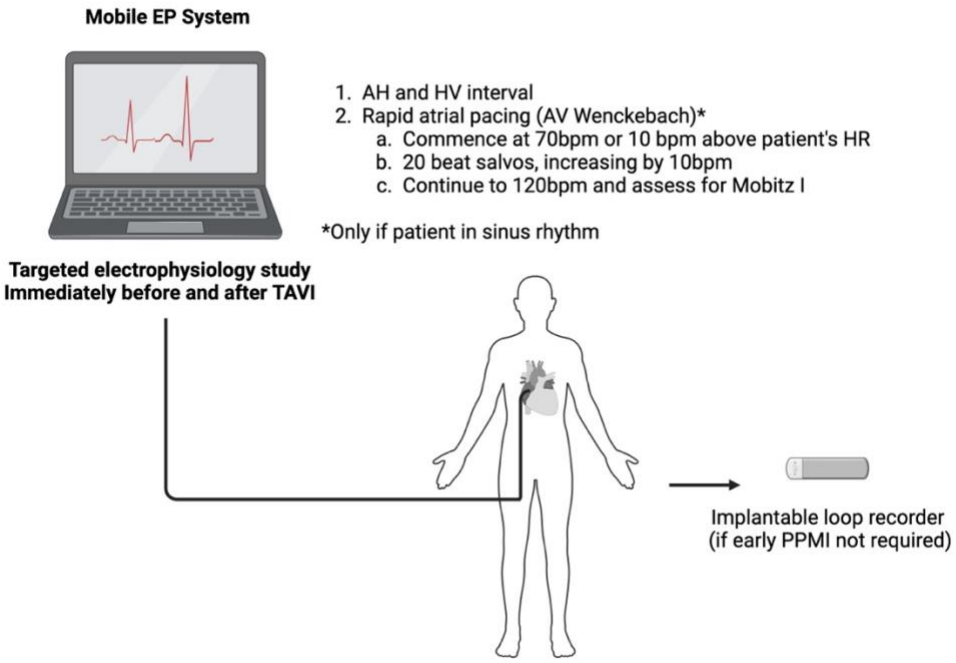
BMI: body mass index; STS: Society of Thoracic Surgeons Risk Score; MSL: membranous septum length; LVOT: left ventricular outflow tract; DLZ: device landing zone; NCC: non-coronary cusp; RBBB: right bundle branch block; LBBB: left bundle branch block; AF: atrial fibrillation; HV: His-Ventricle Interval; CHB: complete heart block; AVW: Atrioventricular Wenckebach; Δ: delta (change)

Score	*Predicted risk of PPMI at 1 year*	*Predicted risk of Early PPMI*	*Predicted risk of Late PPMI* **In those without early PPMI*
0	2/76 (2.6%)	1/76 (1.3%)	1/75 (1.3%)
1	17/78 (21.8%)	10/78 (12.8%)	7/68 (10.3%)
2	18/40 (45.0%)	13/40 (32.5%)	5/27 (18.5%)
3	5/6 (83.3%)	3/6 (50.0%)	2/3 (66.6%)

Supplementary Table S6: CONDUCT TAVI Score distribution across cohort, and risk of PPMI at 1 year, risk of early (<48 hours) PPMI, and late (>48 hours – 1 year) PPMI.
PPMI: permanent pacemaker implantation.

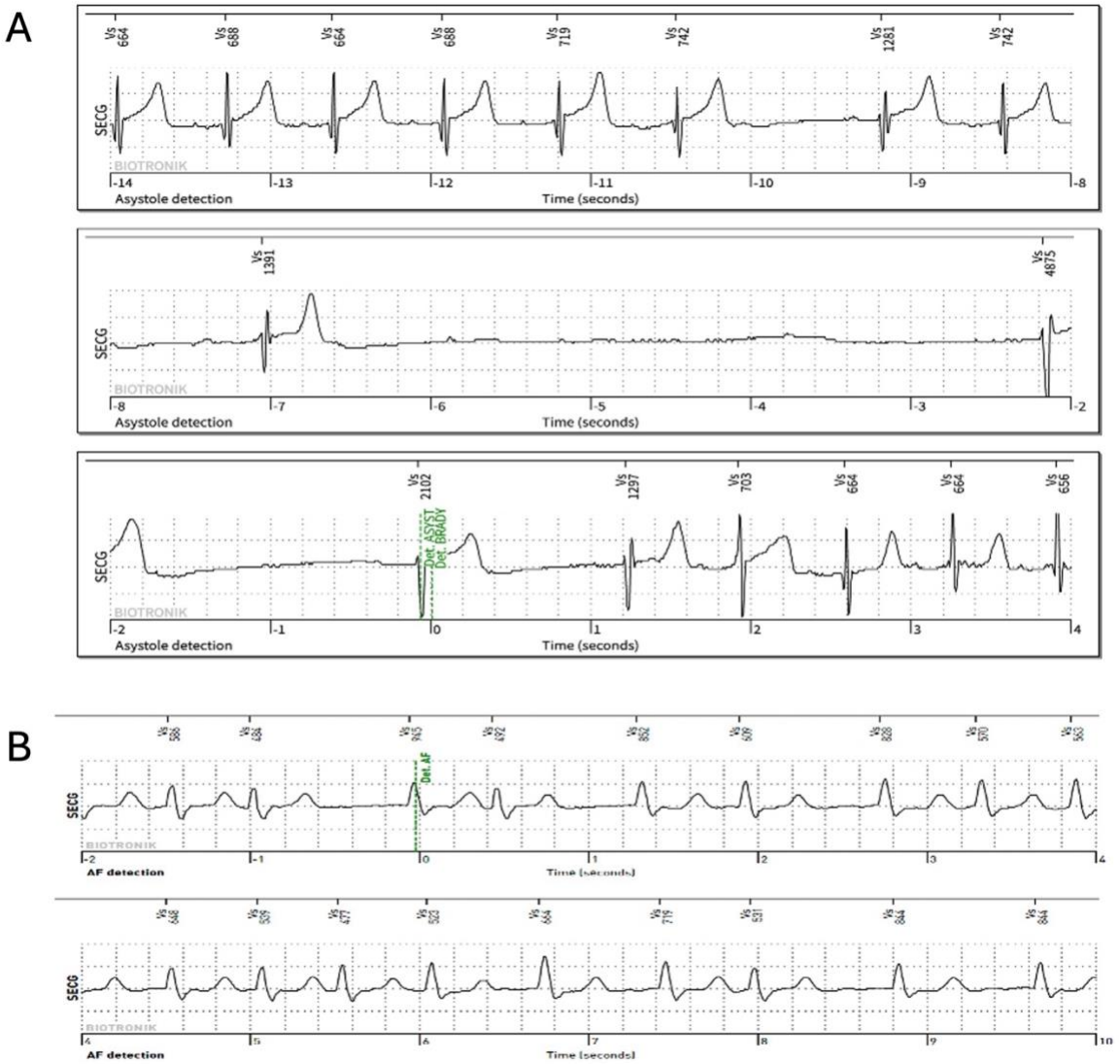


Supplementary Figure 1: Schematic diagram explaining relevant anatomical characteristics and the “device landing zone (DLZ”)

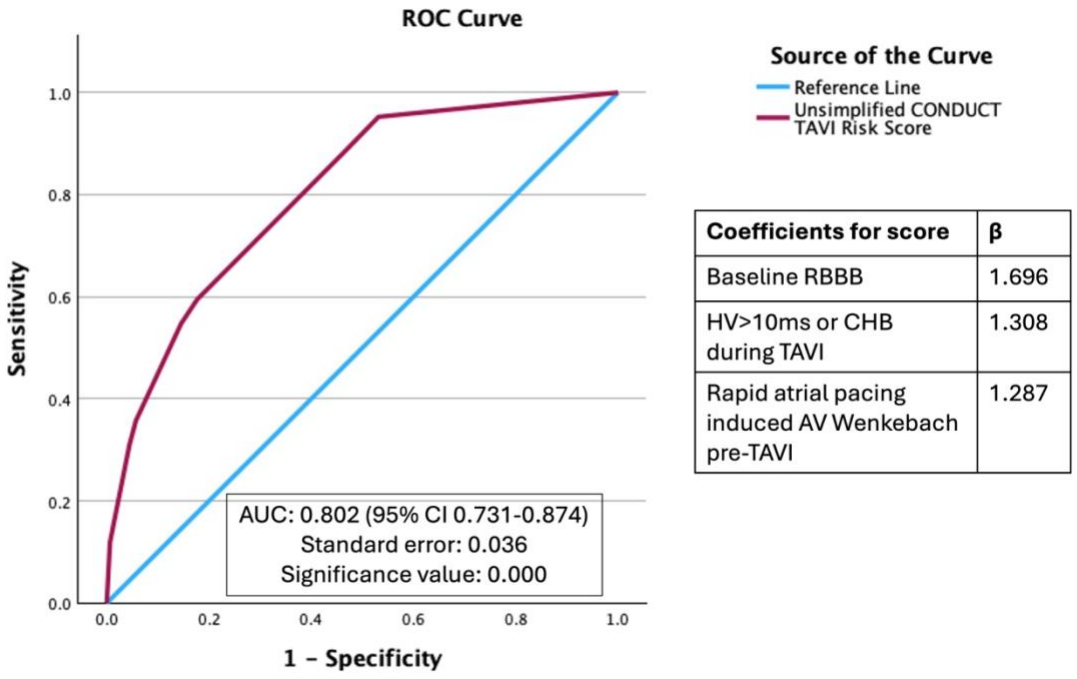


Supplementary Figure 2: Schematic diagram explaining EP system pacing protocol and subsequent pathway.

Supplementary Figure 3: Setup of mobile EP system on right side of patient table in catheterisation laboratory, with quad polar electrophysiology catheter connected to system.



Supplementary Figure 4: A: Example of loop recorder readings of patient with delayed HGAVB (patient 120/200). B: Example of loop recorder readings of patient with new-onset atrial fibrillation (patient 185/200).



Coefficients for score	β
Baseline RBBB	1.696
HV>10ms or CHB during TAVI	1.308
Rapid atrial pacing induced AV Wenkebach pre-TAVI	1.287

Supplementary Figure 5: Receiver operator characteristic (ROC) Curve for the unsimplified CONDUCT-TAVI Risk Score, with the relevant beta-coefficients listed and statistical performance metrics included.

SECTION III: EXTENDING THE SCOPE OF THE CONDUCT-TAVI STUDY THROUGH POST-HOC ANALYSES

Section Introduction: Post-Hoc Analyses In the CONDUCT-TAVI Prospective Cohort

Section III of the thesis builds on the foundation of the comprehensive prospective CONDUCT-TAVI study (Chapter 6) and explores three complementary avenues of post-hoc analysis. Collectively, Section III aims to refine risk prediction, review mechanistic insights, and critically examine long-standing assumptions regarding the interplay between aortic stenosis, TAVI and associated arrhythmias.

Chapter 7 aims to improve the anatomical prediction of atrioventricular block after TAVI. Using patient-specific CT aortography, it proposes a reliable and reproducible estimation of the course of the conduction axis *across* the cardiac cycle (systole and diastole) and introduces the concept of conduction system circumferential orientation as a novel predictor of conduction system injury. By integrating these advanced anatomical markers with traditional non-invasive procedural risk factors, this chapter refines the prediction algorithm for pacemaker implantation and extends the work of CONDUCT-TAVI towards more personalized and non-invasive risk assessment.

Chapter 8 shifts focus to atrial fibrillation, examining the incidence and predictors of new-onset atrial fibrillation (NOAF) after TAVI. Beyond conventional imaging approaches, the study incorporates routine pre-TAVI CT aortography with advanced computational methods, including machine learning-based semi-automated chamber segmentation and statistical shape analysis, to provide a detailed characterization of atrial geometry. These hypothesis-generating results lay the groundwork for future investigations into structural markers that may help identify patients at high risk of developing NOAF.

The final chapter in this section (Chapter 9) challenges the long-standing assumption of a causal link between calcific aortic stenosis and impaired baseline atrioventricular conduction (irrespective of TAVI). By combining baseline clinical cohort data from the CONDUCT-TAVI population with Mendelian randomization analyses, this study bridges clinical and genetic evidence to interrogate the nature of this association. The findings underscore a need for modern studies to re-assess the mechanistic relationship between aortic valve calcification and nodal conduction.

Taken together, this section aims to extend the scope of CONDUCT-TAVI beyond its primary analyses to further address questions of prediction, mechanism and causality of arrhythmias associated with aortic stenosis and TAVI.

CHAPTER 7: Enhanced Prediction of Pacemaker Implantation Post-TAVI Using Pre-Procedural CTA, ECG, Device Characteristics, and Fluoroscopic Implant Depth: A Post-Hoc Analysis of CONDUCT-TAVI

This chapter includes work that is currently under peer review. It has been accepted for an oral presentation at TCT (Transcatheter Cardiovascular Therapeutics) being held in San Francisco, USA in October 2025.

Author attribution statement:

I was the first author involved with the conceptualisation of the study as a post-hoc analysis of CONDUCT-TAVI. I primarily performed the data collection, analysis, follow up and manuscript writing. I am grateful for our collaboration with Professor Shlomo Ben-Haim and Professor Justin Tretter from Hobart Healthcare (London, United Kingdom) for additional analyses based on their uniquely developed and previously validated CT-A methods for estimating the conduction system pathway, including the atrioventricular node, Bundle of His and origin of the left bundle branch – described in further detail in the manuscript below.

Enhanced Prediction of Pacemaker Implantation Post-TAVI Using Pre-Procedural CTA, ECG, Device Characteristics, and Fluoroscopic Implant Depth

Running title: Diastolic CTA Metrics for PPI Prediction

Karan Rao,[1,2] Justin T. Tretter,[3] Tarikh Asyraf,[3] Stefano Spaziani,[3] Ravinay Bhindi,[1,2] Shlomo Ben-Haim[3]

[1] – Department of Cardiology, Royal North Shore Hospital, Sydney, New South Wales

[2] – University of Sydney, Sydney, Australia

[3] – Hobart Healthcare Research Institute, London, UK

Disclosures: Tarikh Asyraf and Stefano Spaziani are CARA Medical employees; Justin T. Tretter is a consultant for CARA Medical, Ltd.; Shlomo Ben-Haim is the founder of CARA Medical, Ltd. The other authors have no relationships relevant to the contents of this paper to disclose.

Keywords: Computed tomography angiography (CTA); Cardiac conduction system; Pacemaker; Right bundle branch block; Transcatheter aortic valve implantation (TAVI)

Word count: 4576 words

7.1 Abstract

Background

Permanent pacemaker implantation (PPI) for atrioventricular block complicates ~15% of transcatheter aortic valve implantations (TAVI). Current predictors lack patient-specific anatomical context.

Objectives

This study sought to develop a model to predict PPI after TAVI by integrating pre-procedural computed tomography angiography (CTA) estimation of the conduction system with fluoroscopic implant depth and clinical factors.

Methods

We retrospectively analysed 143 TAVI patients with pre-procedural CTA that localized the His bundle and left bundle branch origin relative to the annulus (depth and orientation). Device type, oversizing, and fluoroscopic implant depth (referenced to the His bundle) were recorded. The primary outcome was new PPI within 1 year secondary to atrioventricular block. Multivariable logistic regression identified independent predictors.

Results

PPI occurred in 21% (30/143) of patients. Pre-existing RBBB and greater prosthesis oversizing predicted PPI. Conventional annular implant depth was not predictive, but a deeper implantation relative to the His bundle—especially extending beyond the His bundle position measured in diastole—strongly predicted PPI. Multivariable analysis yielded four independent predictors of PPI: RBBB, self-expanding valve oversizing, implant depth beyond the His bundle (diastole), and a posteriorly oriented conduction axis. The final model (AUC 0.86) outperformed traditional risk models.

Conclusions

Patient-specific CTA estimation of the conduction system identified valve implantation depth relative to the His bundle position in diastole and conduction axis circumferential orientation as novel predictors of post-TAVI conduction risk. Integrating these factors with RBBB and valve oversizing provided more precise PPI prediction.

Condensed Abstract:

Permanent pacemaker implantation (PPI) secondary to atrioventricular block occurs in ~15% of transcatheter aortic valve implantations (TAVI). This study sought to develop a predictive model for PPI by integrating patient-specific pre-procedural CT angiography (CTA) derived conduction system estimation with traditional risk factors. In 143 patients, PPI occurred in 21%. Key predictors included pre-existing right bundle branch block (RBBB), valve oversizing, depth of implant exceeding the His bundle (as measured in diastole), and a posteriorly rotated conduction axis. The final model achieved an AUC of 0.86, offering improved PPI risk prediction, and highlighting the importance of integrating patient-specific conduction system estimation.

7.2 Introduction

Permanent pacemaker implantation (PPI) for high-grade atrioventricular block following transcatheter aortic valve implantation (TAVI) occurs in approximately 15% at 1-year in contemporary cohorts, and up to 30% in certain high-risk cohorts(79, 194). New PPI is associated with adverse clinical outcomes, including greater mortality, increased rehospitalization, and additional healthcare cost(171, 195). As TAVI expands into younger and lower-risk populations, minimizing iatrogenic conduction disease becomes increasingly paramount.

Both patient-related and procedural factors contribute to PPI risk after TAVI(47, 48, 53, 196-202).

Anatomically, the vulnerability of the AV conduction axis, which traverses the inferior margin of the membranous septum, is influenced by the distance from the aortic virtual basal ring, or annulus, to the His bundle and bundle branches(52). A closer relationship has been associated with PPI risk. Despite these insights, conventional pre-procedural risk stratification remains suboptimal, and importantly, the typical fluoroscopic assessment of implantation depth provides a limited and sometimes misleading picture of PPI risk.

Recent anatomical and computed tomography angiography (CTA)-based studies have established standardized and reproducible cardiac CTA methods to estimate the location of the AV node, His bundle, and left bundle branch (LBB) origin related to the aortic annulus(50, 203). Prior studies had focused on estimating a discrete and ambiguous point along the AV conduction axis(47-49, 53, 197). Subsequent application of this more holistic estimation of the AV conduction axis, accounting for not only its depth but also circumferential orientation relative to the aortic valve,

has demonstrated improved pre-procedural PPI risk stratification(204). This study, however, did not account for device implantation depth relative to the estimated conduction axis.

We hypothesized that integrating both patient-specific estimation of the AV conduction axis and relating to device implantation depth, along with traditional procedural metrics would provide more accurate risk stratification than existing risk scores. Specifically, we aimed to clarify how the fluoroscopic implantation depth relative to both the depth and circumferential orientation of the patient's estimated AV conduction axis influences PPI risk, and how this relates to individual patient conduction anatomy in diastole versus systole.

7.3 Methods

Study Population and Design

We studied a retrospective cohort of patients who underwent TAVI at a single high-volume tertiary centre with 1-year of follow up using an implantable loop recorder for continuous rhythm monitoring. The inclusion criteria included: presence of severe symptomatic aortic stenosis and availability of pre-procedural cardiac CTA of sufficient quality for 3D conduction system estimation. Patients with a prior cardiac device or prior surgical aortic valve replacement were excluded. Between 2021 and 2023, 200 consecutive TAVI cases meeting these criteria were assessed, and 143 were included in the analysis. **Figure 7** summarizes patient selection. Clinical, ECG, and procedural data were obtained from patient medical records and procedural database. There were no significant differences between excluded and included patients **Supplemental Table 1**. This study was approved by the local institutional review board, and all patients provided consent for the TAVI procedure and associated data collection. For this retrospective analysis of de-identified data, specific consent for the study was waived per IRB policy.

CTA-Based 3D Conduction System Estimation

All patients underwent ECG-gated cardiac CTA prior to TAVI as is standard of care, for procedural planning and valve sizing. All images were de-identified and digitally transferred to a core lab at CARA Medical for retrospective assessment. We applied previously established methods for estimating the location of the proximal AV conduction axis(50) **(Supplemental Figure 1)** using a proprietary software platform (CARA Metis, CARA Medical, Ltd.) designed for this purpose.

The location of the AV node (point A), His bundle course (point B), and LBB origin (point C) were estimated, and the vertical distance ("height") measured relative to the aortic root (**Supplemental Table 2**). Intraobserver and interobserver variability were previously assessed for the CARA Medical core lab reporting excellent intraclass coefficients for these variables (≥0.78)(50). Of note, the aortic annular plane was defined on CTA by points at the aortic surface of the leaflet nadir to better correspond with the annular plane perceived by aortic angiography during the TAVI procedure. We also measured distances between points (for example A–B distance which roughly corresponds to the length of the His bundle). In addition, the circumferential orientation of the conduction axis relative to the aortic valve was quantified. We defined "point X" as the centre of the commissure between the right-coronary and non-coronary aortic leaflets (RCL–NCL commissure). We then measured the angle formed at the centre of the annulus between the line pointing toward point X and the line pointing toward the midpoint of B–C (the estimated transition between the His bundle and LBB origin, or His-LBB axis). This X–midpoint B–C angle describes how rotated the conduction axis is relative to the RCL–NCL

commissure. A negative angle (if the His-LBB origin axis is positioned posterior to the RCL-NCL commissure) indicates the conduction axis is more *posterior* (closer to the NCL), whereas a positive angle (if the axis is positioned anterior to the RCL-NCL commissure) indicates a more *anterior* orientation (closer to the NCL). We also noted the angle between the non-coronary leaflet with both midpoint B–C (NCL–mid B–C angle) and the centre of the inferoseptal recess (NCL-point i), respectively.

For most patients, the CTA phase used was mid-diastole (70 or 80% R–R interval) to minimize motion; if diastolic images were of poor quality, systolic-phase images were alternatively used. The phase of annotation was accounted for.

Procedural Data and Implantation Depth

Procedural details were collected, including TAVI device type (balloon-expandable vs. self-expanding) and size. Fluoroscopic implantation depth was measured on final deployment angiograms. Depth was defined as the length (mm) of prosthesis frame extending below the lowest attachment point of the native leaflets (annular plane) into the left ventricular outflow tract, typically measured at the non-coronary leaflet on an annular plane or cusp-overlap view. A positive depth indicated the prosthesis extended below the annulus (into the ventricle), whereas a negative value (if observed) would indicate a supra-annular position (none in our cohort had negative depth). Depth was first measured conventionally relative to the annulus (we refer to this as **annulus-based depth**). Fifteen missing depth values were imputed by multiple imputation with predictive mean matching using device type and size. Five datasets were pooled for

analysis, and imputed values were consistent with observed data; complete-case sensitivity analyses gave similar results.

We then computed the depth relative to each conduction landmark by subtracting the landmark's CTA-derived height from the fluoroscopic depth. For example, *depth from point B* = (fluoroscopic depth from annulus)– (point B height from annulus). Thus, a depth from point B of 0mm would mean the prosthesis extends exactly to the level of the His bundle; a positive value means the prosthesis extends deeper (inferior to the His bundle), and a negative value means the prosthesis remains superior to the His bundle.

We defined **oversizing** as the difference between the nominal implanted valve diameter and the measured native annulus diameter from CTA, divided by native annulus diameter, expressed as percentage.

Outcome Definition

The primary endpoint was PPI within 1 year after TAVI due to procedure-related conduction disturbance (high-grade AV block). In the absence of persistent high-grade AV block immediately post procedure, all patients received an implantable loop recorder with 1-year of follow up via home monitoring. All detected arrhythmias were co-adjudicated by an electrophysiologist and a cardiac technician blinded to the patients pre-TAVI anatomical, procedural and electrical characteristics. PPI performed within 48 hours of TAVI was classified as early PPI and was performed for persistent or symptomatic high-grade AV block or for alternating left and right bundle branch block. PPI occurring after 48 hours was classified as late PPI and was performed

for any transient or persistent high-grade AV block, regardless of symptoms(205). Cases of pacemaker implantation for indications other than high-grade AV block were excluded.

Statistical Analysis

Continuous and categorical variables are presented as median [IQR] and counts (percentages), respectively. Baseline characteristics and key anatomical measurements were summarized. Measurements obtained in systole and diastole were compared using Wilcoxon rank-sum tests. In univariable models, outcome was regressed on clinical, anatomical, and procedural variables; predictors with $p<0.10$ or deemed clinically important were entered in multivariable models with stepwise selection. Given few PPI events (n=30) and a strong predictor (RBBB), Firth's penalized likelihood was employed to avoid separation(206, 207). Predictor interactions were evaluated with and without main effects: interaction-only structure was retained where it enhanced interpretability(208) and resulted in superior performance without compromising calibration (e.g. effects of device depth from conduction system dependent on CTA phase used to obtain the measurements; effects of oversizing dependent on self-expanding v balloon-expandable device mechanism). The final model was selected based on Akaike Information Criterion (AIC) and area under the receiver-operating characteristic curve (AUC). The final model was compared to simpler models (e.g., only clinical variables or annular depth) and Emory score(209) using bootstrap tests of 10,000 replicates for paired ROC curves. Calibration was analysed utilizing Brier score, Hosmer-Lemeshow test, calibration plot, intercept and slope. We performed 5-fold cross-validation with 10 repeats, summarizing calibration metrics across folds. Additionally, we *optimism*-corrected model performance using 1,000 bootstrap replicates to reflect expected performance on new data.

Associations were verified in time-to-event analysis using Cox proportional hazards model based on same predictor structure. Kaplan-Meier curves, hazard ratios (HR) and model concordance are reported. All tests were two-tailed with $\alpha=0.05$. Analyses were performed in R v4.0.

7.4 Results

Patient Characteristics and Conduction Landmark Measurements

Table 1 summarizes demographics, clinical and CTA-based findings of the studied cohort. Among the 143 patients, the median age was 83 years (IQR 9.3), and 53 patients (37%) were female. Baseline RBBB was present in 22 patients (15%), and 32% had first-degree AV block. Self-expanding TAVI prostheses were used in 85 cases (59%), and balloon-expandable valves in 58 cases (41%). The median percent oversizing compared to native annulus size was 15.6 % (IQR 18.1) overall.

The conduction system was estimated in 69% of patients using systolic-phase images and in 31% using diastolic-phase. The estimated AV node (point A), His bundle course (point B), and LBB origin (point C) were located at median depth of 10mm (IQR 5.7), 5.0mm (IQR 3.4), and 2.5mm (IQR 2.9) below the aortic valve annulus. The median angle between the RCL–NCL commissure and the His–LBB origin axis (X–mid B–C angle) was –3.5° (IQR 13.3°), indicating that while the conduction axis is commonly positioned under the right and non-coronary leaflet commissure (angle near 0°), there was marked variability in deviation towards non-coronary (negative angle) or right-coronary leaflets (positive angle).

Procedural Outcomes and Pacemaker Incidence

All patients underwent successful transfemoral TAVI with conscious sedation. The median fluoroscopic annular implantation depth was 3.7mm (IQR 2.7mm). Early PPI (≤48 hours) was required in 19 patients (13% of the cohort; 63% of all PPI), and an additional 11 patients (8% of the cohort; 37% of all PPI) received a pacemaker >48 hours up to 1-year follow-up (**Figure 8**). Overall, 30 of 143 patients (21%) ultimately required PPI for high-grade AV block.

Univariate Predictors of PPI

Simple binary predictors of post-procedure PPI are reported in

Table 2. Several conventional risk factors were confirmed. This included device oversizing, with the trend illustrated in **Figure 9**, which shows PPI rates climbing precipitously once oversizing exceeds 10%.

Regarding the novel estimation of the conduction axis, patients with more anteriorly oriented conduction axis (more *positive* X–midpoint BC angle) were less likely to require a PPI compared to those with more posteriorly oriented (more *negative* angle) conduction axis (OR 0.96 per degree, 95% CI 0.93–1.00; p=0.036).

Differences in Systolic vs. Diastolic Measurements

Prior to multivariable modelling, we analysed the differences in CTA-derived measurements between patients evaluated in systolic (n=99) and diastolic (n=44) phases (**Table 3**). During systole, the His bundle and bundle branches were located deeper within the left ventricle compared to diastole, where positioning was more basal (closer to the annulus). Specifically, the median depth of point B (His bundle) was 5.3mm below the annulus in systole versus 3.9mm in

diastole (p=0.003). Similarly, point C (LBBB) was measured at 3.0mm in systole compared to 1.7mm in diastole (p=0.012). **Figure 8** graphs the conduction axis (His–LBB origin axis) migrating between the two phases.

As anticipated, the computed *conduction-referenced* device depths also varied by cardiac phase: among cases for whom device depth was computed from point B measurements in *diastole*, the result appeared 1.8mm shallower compared to those for whom depth was computed from *systolic* measurements (p=0.009), thus highlighting the importance of phase-specific depth computation. Given these *dynamic* differences, we constructed predictive models where the effects of *systole*- and *diastole*-referenced device depth were treated separately.

Multivariable Model for PPI Risk

Using penalized multivariable logistic regression, we identified an optimal combination of predictors for PPI (**Table 4**). The final model incorporated four significant independent predictors: (1) the X–midpoint B–C angle (conduction axis circumferential orientation) [aOR 0.95 per 1° increase (95% CI 0.91–0.99, p=0.012)] (2) pre-existing RBBB [aOR 14.0 (95% CI 4.56–49.1, p<0.0001)], (3) fluoroscopic device depth relative to point B in *diastole* [aOR 1.52 per 1mm (95% CI 1.12–2.17, p=0.006)], and (4) prosthesis oversizing (for self-expanding valves) [aOR 1.07 per 1% increment (95% CI 1.02–1.13, p=0.007)]. In the same model, *systole*-referenced device depth from point B was not associated with the outcome (p=0.72). **Figure 11** demonstrates the difference in association of systole- and diastole-referenced device depth from the conduction system axis and pacemaker implantation. Furthermore, oversizing of balloon-expandable devices was not significantly associated with the outcome (p=0.49), although a

limited degree of oversizing was observed in this subgroup, per standard practice (maximum 14%; median 3.17% (IQR 6.4) compared to 21.5% (IQR 8.3) in self-expanding valves, p<0.0001).

This model achieved good discrimination with AUC=0.86 (95% CI 0.77–0.93), demonstrating sensitivity of 83% and specificity of 80% at the optimal probability cutoff (maximizing Youden's index). **Figure 12** presents the final model's ROC curve. The final model was significantly superior to 3 *comparator* models: (1) implant depth alone—without consideration of patient-specific conduction anatomy (AUC: 0.48, p<0.0001); (2) a model based solely on clinical variables (including RBBB, device type, and size; AUC 0.80, p=0.0279); and (3) with addition of fluoroscopic device depth (AUC 0.81, p=0.021). **Figure 13** highlights the incremental benefit of including the CTA-based conduction depth and circumferential orientation assessment.
In our sample, the Emory score demonstrated an OR of 2.99 (95% CI 2.91–4.73) per 1 point increase for predicting PPI post-TAVI (AUC =0.79), which was significantly inferior to the final model (p=0.0187). The model was not substantially overfitted and calibration remained adequate following optimism correction (**Supplemental Figure 2** and **Error! Reference source not found.2)**. An interactive risk calculator based on the final model is available. **Supplemental Table 4** contrasts the closely *'competing'* models.

In time-to-event analysis, patients with RBBB pre-TAVI were at 6-fold greater risk of requiring PPI (HR 6.5 [95% CI 3.2–13.4]; **Supplemental Figure 3**). In a Cox proportional hazards model repeating the final model structure, a more positive X-mid B–C angle was protective (aHR 0.95 [0.92–0.98], p=0.003), pre-existing RBBB strongly increased risk (aHR 8.01 [3.63–17.7],

p<0.001); deeper *diastole-referenced* device implantation (aHR 1.32 [1.09–1.61], p=0.005) and higher oversizing of self-expanding valves (HR 1.06 [1.02–1.11], p=0.007) were significant predictors, while systolic depth and oversizing of balloon-expandable valves were not (**Error! Reference source not found.Supplemental Table 5** and **Supplemental Figure 4**). Model concordance was 0.825 (95% CI 0.749–0.901).

7.5 Discussion

In this study, we developed a novel risk prediction model for PPI after TAVI that integrates both the circumferential and vertical orientation of the estimated 3D CTA-derived conduction system relative to the native aortic valve and implanted device, with procedural and clinical factors. The key findings are as follows:

1. Patient-specific implant depth relative to the His bundle predicted PPI risk, whereas conventional depth measured from the annular plane was not predictive.
2. Diastolic-gated measurements of the conduction axis, as opposed to traditional end-systolic-gated measurements, were more predictive of PPI in our cohort, which we hypothesize were secondary to the His bundle translating basally towards the annulus during diastole, as opposed to deeper ventricular migration in systole.
3. The presence of baseline right bundle branch block (RBBB) was independently associated with 14-fold increased odds for PPI.
4. Oversizing of self-expanding valves was independently associated with PPI risk, whereas oversizing of balloon-expandable valves did not exhibit significant predictive value.
5. An anteriorly orientated (positive X-midpoint BC angle) conduction axis was protective for PPI risk, whereas a posterior orientation increased risk.

Implantation Depth: Conventional vs. Anatomy-Referenced

Implant depth has long been discussed as a modifiable risk factor for PPI. Numerous studies have associated deeper valve implants with higher PPI rates, secondary to amplified interaction with the membranous septum and the underlying conduction axis(201). Notably, we found that the conventional fluoroscopic *annular depth* alone **did not** correlate with PPI in our cohort. This underscores that patient-specific anatomic variation of the conduction axis may confound this raw depth measurement. Our findings aim to refine the concept of implant depth, and as suggested first by Jilaihawi *et al* (49), our results reiterate that implant depth surpassing the patient's native His/LBB axis, is the more relevant metric. Furthermore, our CTA-based estimation assesses discrete points along the proximal AV conduction axis, from AV node, to His bundle, to LBB origin, providing improved standardization and reproducibility towards this more granular assessment(50, 210).

These findings also align with recent reports suggesting conventional fluoroscopic depth assessment can be misleading. A recent study showed only limited correlation between fluoroscopy and post-procedure CT derived implantation depths, with the fluoroscopy systematically underestimating true depth, translating to a weaker association with PPI risk compared to more precise CT derived measurements(61). In practice, operators can be misled by fluoroscopic estimation due to the projection angle or radiographic foreshortening. More recently, optimized imaging with the cusp-overlap view (which eliminates foreshortening and aims to isolate the NCL) can help operators reliably gauge device position relative to the conduction axis. A recent meta-analysis of 3,647 patients found that the cusp-overlap projection

led to a 46% relative reduction in PPI and a higher final valve position compared to the traditional three-cusp view(211). Likewise, the Optimize PRO study reported a 30-day PPI incidence of only 9.8% when using a standardized cusp-overlap guided implantation protocol in self-expanding valves(62). Our results demonstrate that the His bundle is the key reference point for implantation depth, ands calls for precise anatomy-guided implantation strategies—with a combination of individualized CTA planning (using conduction system landmarks) and improved real-time and appropriate fluoroscopic visualization.

The dynamic association between His Bundle / LBB axis and the aortic annulus

Our analysis of systolic and diastolic-gated CTA demonstrates a dynamic septal anatomy which has not been previously reported to the best of our knowledge. The membranous septum translates basally in diastole, which brings the His bundle significantly closer to the annulus. Diastolic His bundle measurements showed greater predictive value for PPI risk than systolic measurements, indicating that routine end-systolic imaging—commonly used to reduce motion artifact and maximize annular dimensions—may underestimate the true proximity of conduction tissue.

Based on these findings, we recommend inclusion of a mid-diastolic phase in pre-TAVI CT when feasible, with conduction landmark measurements performed in diastole.

The influence of circumferential conduction system rotation on PPI risk

We also identified conduction axis orientation as a modest but novel factor. This supports prior anatomical observations which noted predicted relationships related to variation between the circumferential orientation of the conduction axis and membranous septum with variability in the

rotational position of the aortic root and corresponding size of the inferoseptal recess(212). We quantified this circumferential orientation of the conduction axis relative to the aortic root as the X–mid B–C angle and found that a more anteriorly oriented conduction axis (trending towards a positive angle) was associated with *lower* risk of PPI (~5% lower odds per degree of clockwise rotation). This finding raises the question of whether a more specific catheter position for deployment or a specific circumferential orientation of the prosthesis relative to that of the conduction axis could reduce radial forces on the conduction axis and avoid its damage. At a minimum, appreciating the rotational conduction anatomy may provide better risk stratification.

Limitations

Our study is a retrospective, single-centre analysis with a modest sample size and number of PPI events (n=30), which necessitated the use of penalized regression to mitigate small-sample bias. While the model performed well internally, external validation is an ongoing pursuit to ensure generalizability. Additionally, the primary focus of this study was the logistic regression model, chosen for its ease of interpretation in clinical practice, where the need for a PPI is often considered a binary outcome regardless of the exact timing. A supplemental time-to-event analysis confirmed that the same predictors remained significant over follow-up. This approach was also appropriate given the study's sample size constraints. A larger time-to-event study will be needed to investigate the exact timing of PPI in more detail, which could guide clinical triage decisions.

We included late PPI events up to 1 year, which is a strength in capturing the full scope of TAVI-related conduction issues. However, it is possible that a few late pacemakers were due to progressive native conduction disease rather than iatrogenic.

7.6 Conclusion

Integrating CT-based patient-specific 3D conduction-system anatomy estimation with procedural variables improves prediction of pacemaker requirement after TAVI. Our model—which adds novel spatial metrics of the conduction axis (circumferential orientation and dynamic depth) relative to device implantation depth, to established predictors such as baseline RBBB and oversizing — achieved high accuracy (AUC 0.86). These results support individualized procedure planning (device choice, sizing, and implantation depth/orientation) to reduce iatrogenic PPI, particularly as TAVI expands to younger, low-risk patients. Larger multicentre studies and interventional trials are needed to validate these findings and determine whether targeted modifications in high-risk anatomies lower PPI incidence.

Clinical Perspectives

Competency in Medical Knowledge:

Permanent pacemaker implantation (PPI) occurs in 15-20% of patients following transcatheter aortic valve implantation (TAVI). However, existing risk prediction models remain imprecise. Integrating patient-specific and cardiac-phase stratified CT angiography for estimating conduction system anatomy, alongside traditional procedural variables, significantly enhances the prediction of PPI.

Translational Outlook 1:

Following prospective multicentre validation, our proposed PPI prediction algorithm could be incorporated into routine TAVI planning, thereby improving periprocedural risk stratification.

Translational Outlook 2:

Future work should refine automated tools which overlay our proposed individualised CT angiography derived conduction landmarks into fluoroscopy to guide precise real-time implantation depth.

7.7 Tables and Figures

Table 1. *Clinical & demographic characteristics of the cohort (N=143).*

Variable	Median / n	IQR / %
Age (years)	83.0	[9.3]
Gender (Female)	47	37%
CTA assessed in systole	99	69%
RBBB	22	15%
Iº AVB	37	32%
Bileaflet valve	5	3%
Fluoroscopic Device Depth (mm)	3.7	[2.7]
Conduction System Landmarks		
Point A height (mm)	10.0	[5.7]
Point B height (mm)	5.0	[3.4]
Midpoint B-C height (mm)	3.9	[3.1]
Point C height (mm)	2.5	[2.9]
B-C length (mm)	8.3	[4.4]
NCL-mid B-C angle (degrees)	57.2	[15.3]
X-mid B-C angle (degrees)	-3.5	[13.3]
i-NCL angle (degrees)	3.0	[17.4]
Leaflet Angular Measurements (degrees)		
XY	112.3	[13.3]
XZ	126.8	[21.2]
YZ	118.8	[14.8]
Leaflet Commissural Angle (degrees)	124.0	[6.7]
*Average native aortic valve annulus diameter (mm)	24.5	[3.4]
Device diameter (mm)	29.0	[3.0]
†Device oversizing (mm)	3.80	[4.4]
πDevice oversizing (%)	15.6	[18.1]
Self-Expanding Mechanism	85	59%
Fluoroscopic device depth (mm)		
Measured from annulus (VBR)	3.7	[2.5]
‡*Computed from Point A*	-6.7	[5.6]
‡*Computed from Point B*	-1.5	[3.8]
‡*Computed from Midpoint B-C*	-0.4	[3.7]
‡*Computed from Point C*	1.0	[3.9]
Outcome: PPI Requirement	**30**	**21%**
Within 48h of TAVI	19	13%
Within 1y follow-up	11	8%

* Calculated as $D_{(average)} = \frac{(D_{max} + D_{min})}{2}$

† Calculated as $Oversizing = D_{(device)} - D_{(average)}$

π Calculated as $\%\ Oversizing = \frac{D_{(device)} - D_{(average)}}{D_{(average)}} \times 100$

‡ Calculated as $H_{(computed)} = H_{(device)} - H_{(point)}$

Table 2. *Simple binary predictors of post-procedure PPI.*

Predictor	OR	95% CI	*p* value
Age (years)	1.02	[0.95–1.09]	0.6236
Gender: Female	0.34	[0.11–0.91]	0.0445
Phase: Systolic	0.71	[0.31–1.70]	0.4323
Native Valve Characteristics			
Bileaflet valve	6.17	[0.98–48.6]	0.0524
[*]Average annular diameter (mm)	1.11	[0.94–1.31]	0.2175
XY	0.97	[0.93–1.01]	0.2133
XZ	0.97	[0.94–1.00]	0.1009
YZ	1.03	[1.00–1.06]	0.0284
Leaflet Commissural Angle (degrees)	1.05	[1.00–1.11]	0.0580
Conduction System Anatomy Landmarks			
Point A height (mm)	0.95	[0.85–1.04]	0.2834
Point B height (mm)	0.94	[0.79–1.09]	0.4306
Midpoint B-C height (mm)	0.91	[0.76–1.08]	0.3106
Point C height (mm)	0.90	[0.75–1.07]	0.2462
B-C length (mm)	1.11	[0.98–1.27]	0.1006
NCL-mid B-C angle (degrees)	1.00	[0.97–1.03]	0.9585
X-mid B-C angle (degrees)	0.96	[0.93–1.00]	0.0355
i-NCL angle (degrees)	1.00	[0.97–1.04]	0.7913
Pre-operative RBBB	11.5	[4.27–33.1]	<0.0001
Pre-operative Iº AVB	0.82	[0.29–2.14]	0.6987
Pre-operative PR interval duration (ms)	1.00	[0.99–1.01]	0.8184
Implanted Device Characteristics			
Device Type: Self-Expanding Mechanism	2.70	[1.12–7.28]	0.0349
Device Diameter (mm)	1.23	[1.10–1.40]	0.0007
[†]Device oversizing (mm)	1.36	[1.15–1.65]	0.0007
[π]Device oversizing (%)	1.07	[1.02–1.12]	0.0033
Fluoroscopic device depth (mm)			
Measured from annulus (VBR)	0.97	[0.77–1.20]	0.7643
[‡]Computed from Point A	1.05	[0.95–1.15]	0.3474
[‡]Computed from Point B	1.03	[0.91–1.18]	0.6248
[‡]Computed from Midpoint B-C	1.05	[0.91–1.20]	0.5205

[*] Calculated as $D_{(average)} = \frac{(D_{max} + D_{min})}{2}$

[†] Calculated as $Oversizing = D_{(device)} - D_{(average)}$

[π] Calculated as $\%\ Oversizing = \frac{D_{(device)} - D_{(average)}}{D_{(average)}} \times 100$

‡ Calculated as $H_{computed} = H_{device\ (fluoroscopic)} - H_{point\ measurement\ (CTA)}$

Table 3. *Differences in point height measurements depending on CTA series used.*

Measurement	*Diastole* (n=44) median	IQR	*Systole* (n=99) median	IQR	***Wilcoxon Rank Sum Test p-value***
Point A height (mm)	9.5	[4.4]	10.4	[5.9]	0.5116
Point B height (mm)	3.9	[2.8]	5.3	[3.2]	0.0030
Midpoint B-C height (mm)	2.9	[2.4]	4.2	[2.8]	0.0029
Point C height (mm)	1.7	[2.7]	3.0	[2.8]	0.0119
B-C length (mm)	8.2	[5.1]	8.6	[4.2]	0.9268
NCL-mid B-C angle (degrees)	56.9	[22.4]	57.3	[14.3]	0.9791
X-mid B-C angle (degrees)	-3.8	[12.7]	-2.4	[13.1]	0.3305
i-NCL angle (degrees)	-1.6	[17.4]	4.1	[18.2]	0.1895
*__Computed device depth__					
from Point A (mm)	-6.3	[5.1]	-6.8	[5.7]	0.5995
from Point B (mm)	-0.1	[3.9]	-1.9	[3.4]	0.0088
from Midpoint B-C (mm)	0.7	[3.1]	-0.7	[3.3]	0.0140
from Point C (mm)	1.9	[3.3]	0.6	[3.9]	0.0466

* Calculated as $H_{computed} = H_{device\ (fluoroscopic)} - H_{point\ measurement\ (CTA)}$

Table 4. *Multiple binary logistic regression predicting PPI using pre-TAVI and procedural data.*

Term	aOR	95% CI	*p value*
Reference level*	1.00		
X-mid B-C angle (per 1º increase)	0.95	[0.91–0.99]	0.0122
RBBB pre-TAVI	14.0	[4.56–49.1]	<0.0001
†Device depth from Point B measured in *diastole* (per 1mm increase)	1.52	[1.12–2.17]	0.0056
†Device depth from Point B measured in *systole* (per 1mm increase)	0.97	[0.81–1.16]	0.7201
Oversizing of Self-expanding device (per 1 % increase)	1.07	[1.02–1.13]	0.0066
Oversizing of Balloon-expandable device (per 1 % increase)	1.07	[0.88–1.36]	0.4900

aOR=adjusted odds ratio

Firth's model chosen to account for potential small-sample bias in RBBB distribution

Discrimination performance was equivalent to standard logistic regression alternative (p=0.996)

* Reference category: device implanted at the level of Point B, ∠X-mid B-C=0º, RBBB absent.

† Computed as procedural fluoroscopic device depth – point B height from pre-procedure CTA

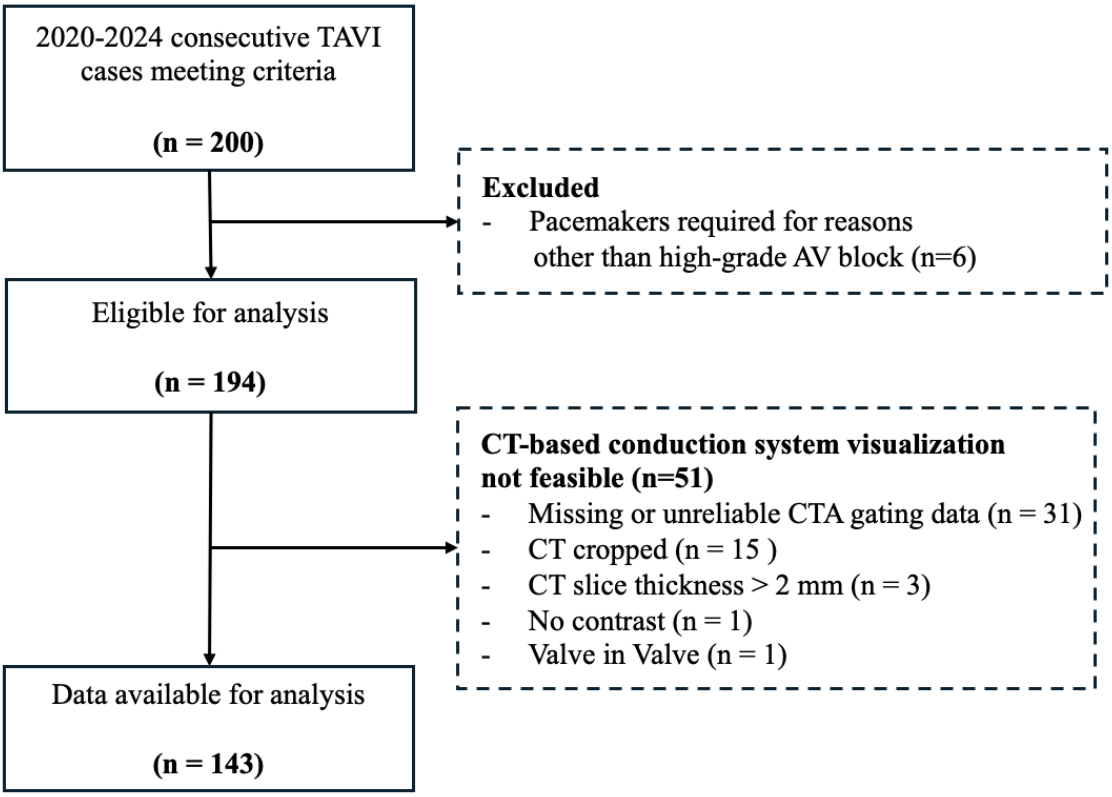


Figure 7. Patient selection flowchart

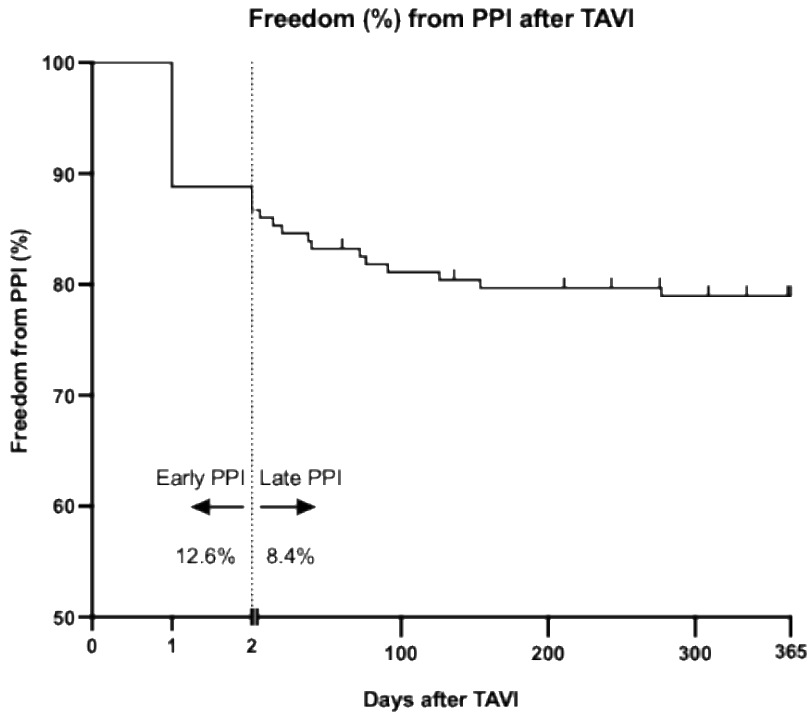


Figure 8. Procedural outcomes and pacemaker implantation incidence

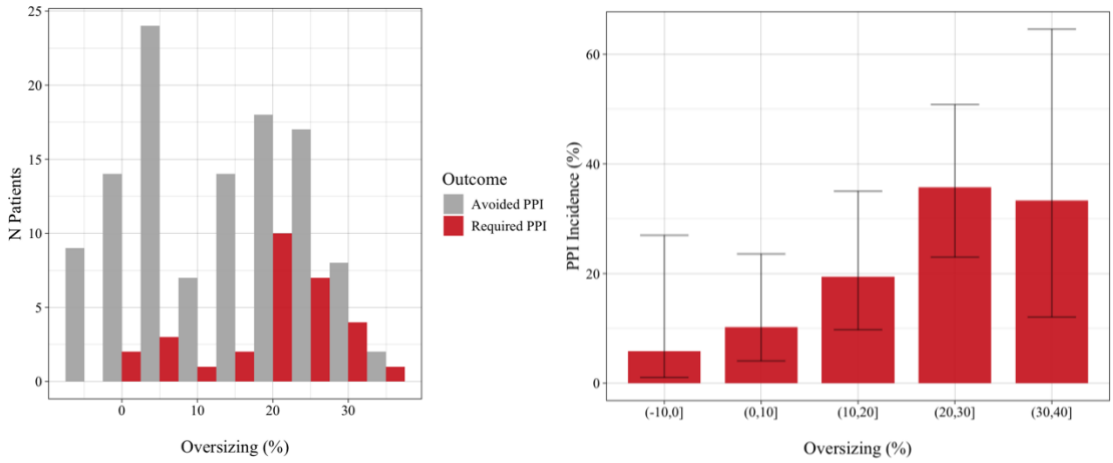


Figure 9. The effect of relative (%) oversizing of implanted devices on the occurrence of PPI. Observed number of cases (left panel) and incidence per 10% increments (right panel); error bars: 95% CI.

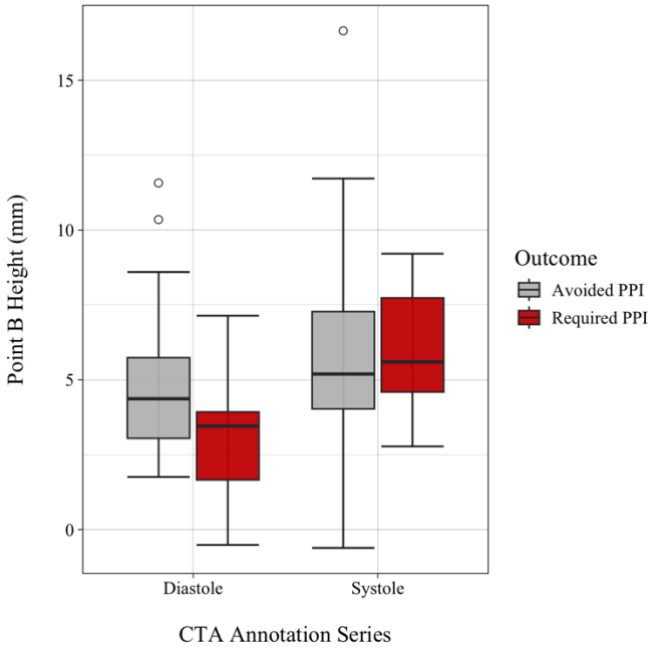


Figure 10. Differences in point heights between outcome groups were more pronounced when assessed in diastole, as opposed to systole, when the underlying structures of the membranous septum 'assume a farther position toward the LV lumen and away from the valve'; error bars: SD.

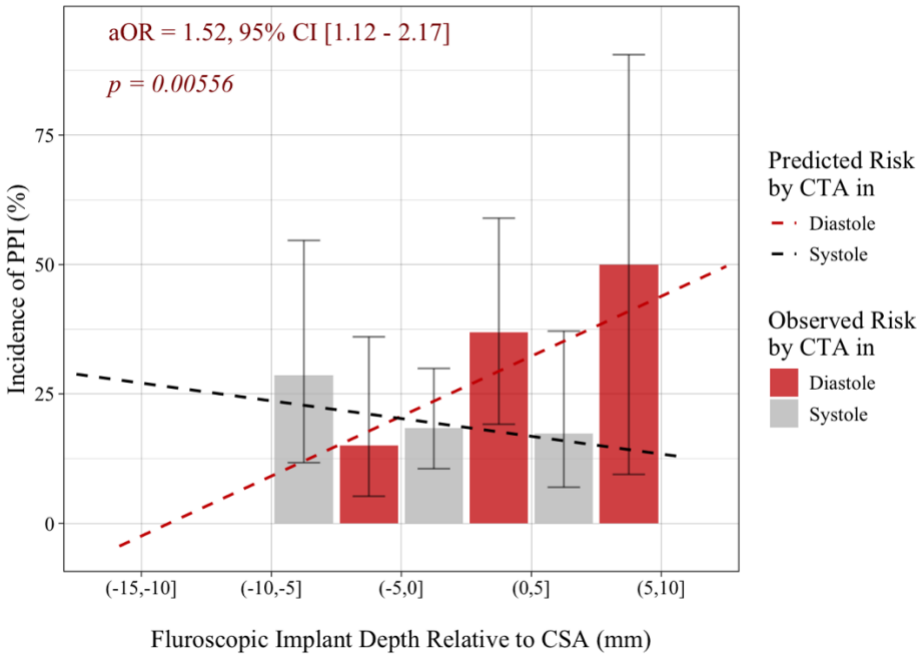


Figure 11. Differences in systole- and diastole-referenced device depth in association with PPI; error bars: 95% CI.

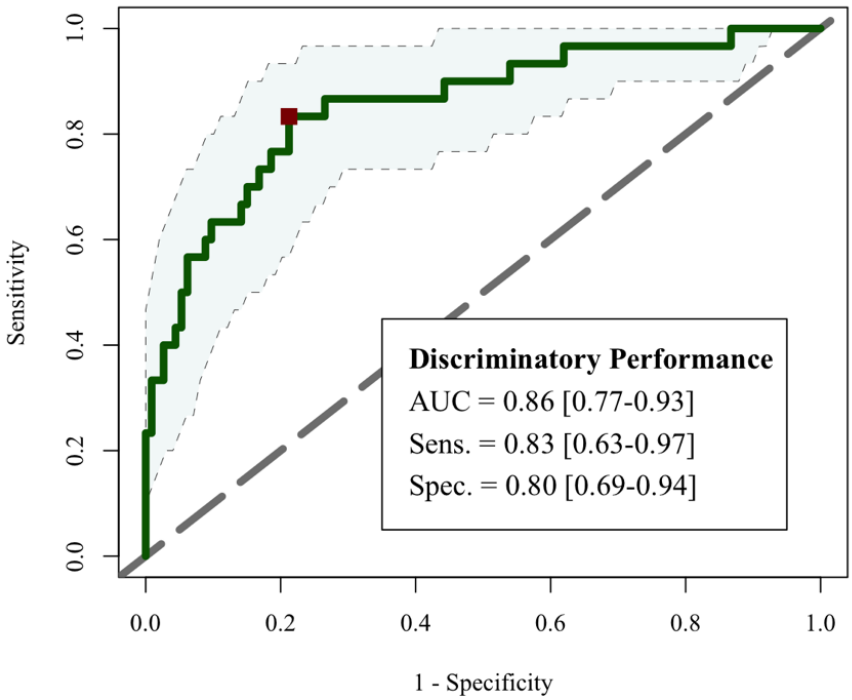


Figure 12. ROC characteristics of the final PPI prediction model. Shaded area: 95% confidence intervals.

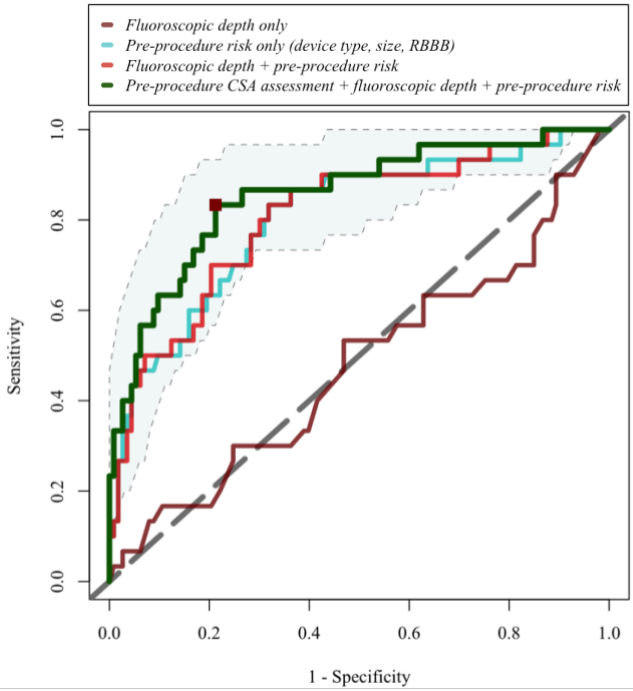


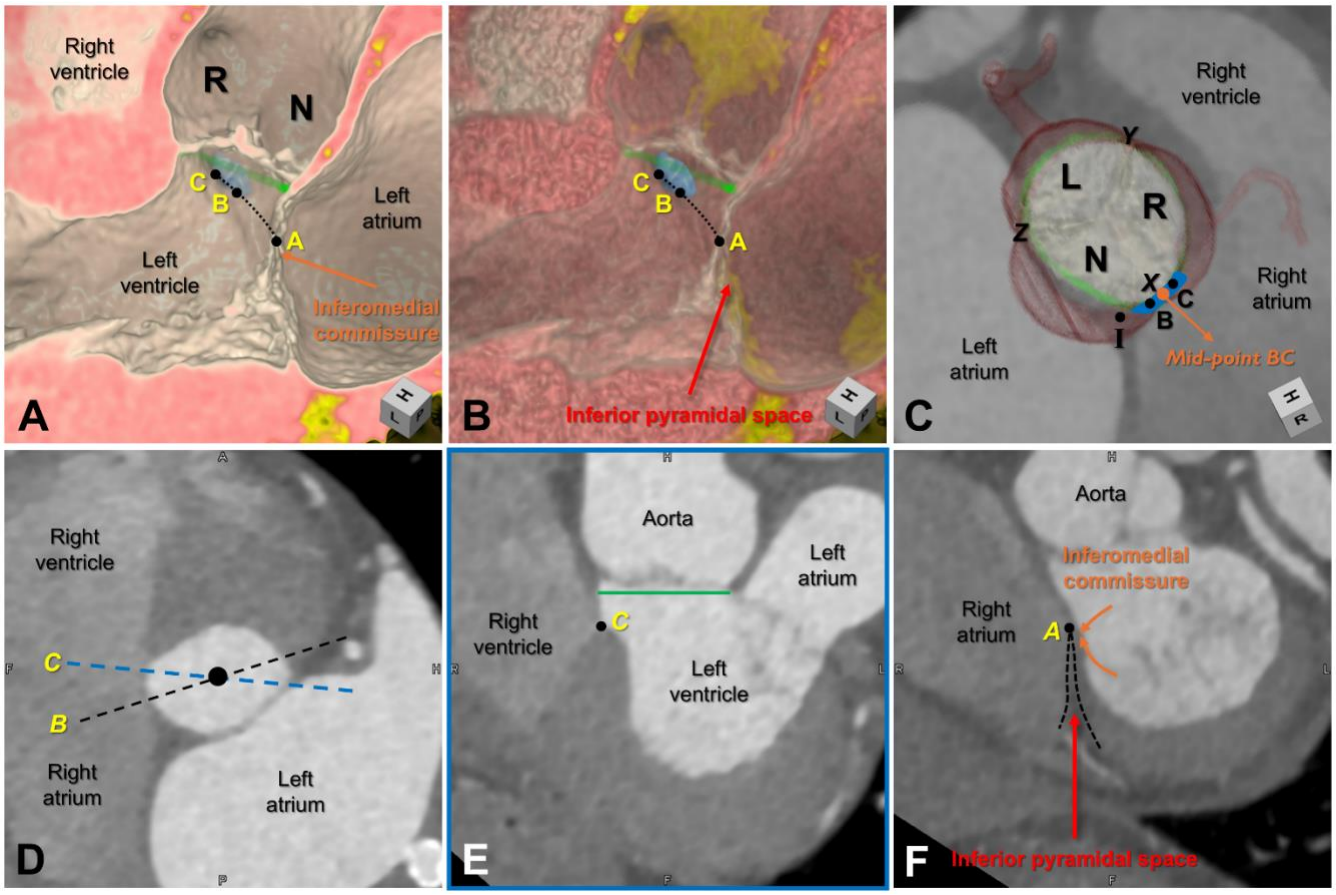
Figure 13. The added value of pre-procedure conduction system axis (CSA) estimation using CTA. Shaded area: 95% confidence intervals of the final model.

7.8 Supplemental Material

Supplemental Table 1. *Comparison of clinical and demographic characteristics of included and excluded participants.*

Variable	Included (n=143)		Excluded (n=51)		p-value
	Median / n	**IQR / %**	**Median / n**	**IQR / %**	
Age (years)	83.0	[9.3]	83.0	[6.0]	0.654
Gender (Female)	47	37%	11	22%	0.840
CTA assessed in systole	99	69%	16	31%	0.495
RBBB	22	15%	6	12%	0.814
Iº AVB	37	32%	12	24%	0.845
Bileaflet valve	5	3%	0	0%	0.333
*Average native aortic valve annulus diameter (mm)	24.5	[3.4]	25.2	[4.0]	0.514
Device diameter (mm)	29.0	[3.0]	29.0	[8.0]	0.413
†Device oversizing (mm)	3.8	[4.4]	4.4	[4.7]	0.320
πDevice oversizing (%)	15.6	[18.1]	18.8	[18.9]	0.391
Self-Expanding Mechanism	85	59%	32	63%	0.398
Fluoroscopic device depth (mm)	3.7	[2.5]	3.3	[2.8]	0.387
Outcome: PPI Requirement	**30**	**21%**	***11**	**22%**	**0.839**
Within 48h of TAVI	19	13%	7	14%	0.811
Within 1y follow-up	11	8%	4	8%	1.000

*The 6 participants who received PPI for non-high grade AV block indications are disregarded in this comparison

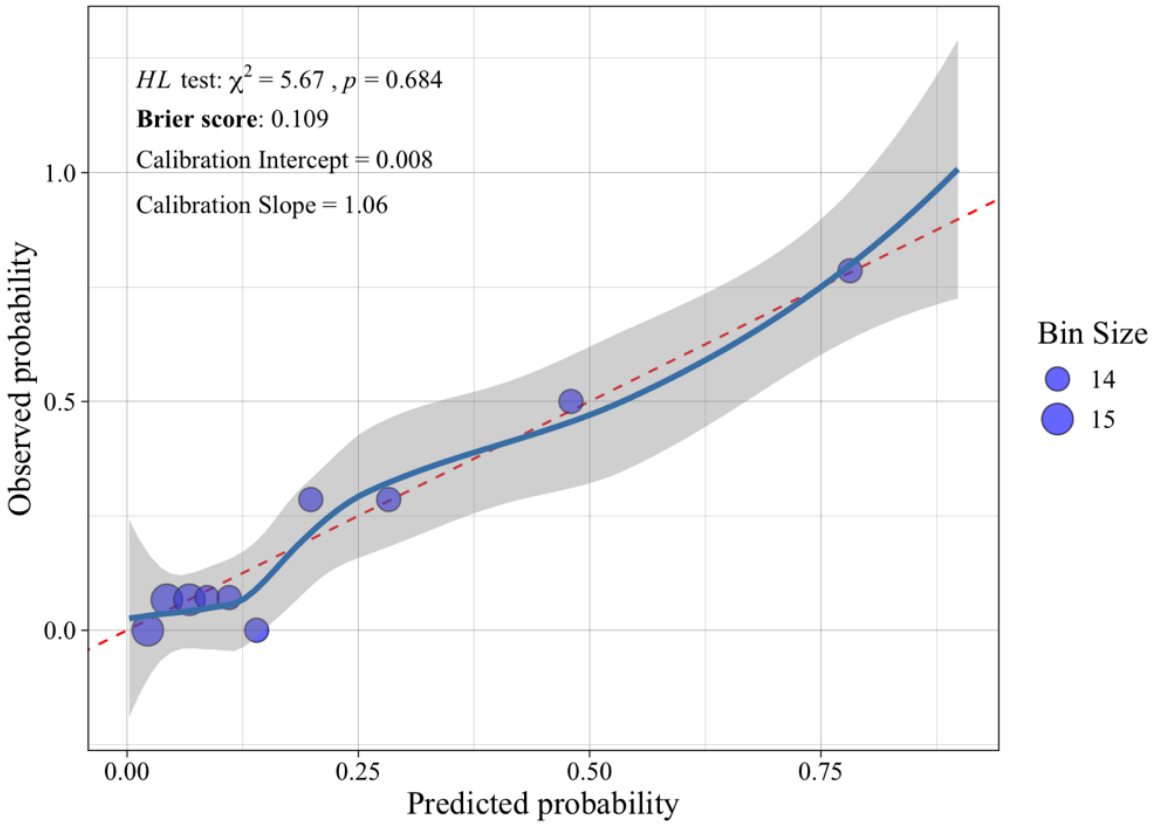


Supplemental Figure 1. Previously established CTA-based methods for estimating the location of the proximal atrioventricular conduction axis.(36) **(A,B)** Three-dimensional reconstruction viewing the left ventricular outflow tract **(A)** with the myocardium transparent **(B).** The estimated location of the atrioventricular conduction axis is depicted (black dotted line connecting Points A, B, and C) relative to the aortic virtual basal ring (green line). The atrioventricular node (Point A) is positioned at the apex of the inferior pyramidal space, adjacent to the inferomedial commissure of the mitral valve. The non-branching bundle courses towards the inferior margin of the membranous septum (Point B, membranous septum coloured blue) giving origin to the left bundle branch anteriorly (Point C). **(C)** A three-dimensional short axis of the aortic root is depicted as viewed from above demonstrating the location of the membranous septum relative to the right (R) and non-coronary leaflet (N) commissure (*X*) and the middle of the roof of the inferoseptal recess (*I*). Using multiplanar reformatting, the short axis of the aortic valve virtual basal ring **(D)** is obtained, with the orthogonal long axis plane across the membranous septum to assess for Point B and Point C **(E)**. A short axis of the mitral valve annulus is obtained, positioning inferiorly **(F)** to identify the inferomedial commissure of the mitral valve and the hypoattenuated apex of the inferior pyramidal space to locate Point A. L, left coronary leaflet; *Y*, left and right coronary leaflet commissure; *Z*, left and non-coronary leaflet commissure.

Supplemental Table 2. *Definition of assessed points in estimating the location of components of the atrioventricular conduction axis.*

Variable	Significance
Point A *Atrioventricular Node*	Estimated location of the atrioventricular node. This point is marked adjacent to the inferomedial commissure of the mitral valve, near the right atrial endocardial surface. The apex of the hypoattenuated inferior pyramidal space is additionally used to help confirm this location.
Point B *His Bundle*	Estimated location of the course of the His (non-branching) bundle. This point is marked at the posterior aspect of the inferior margin of the membranous septum.
Point C *Left Bundle Branch Origin*	Estimated location of the location of the origin of the left bundle branch. This point is marked at the anterior aspect of the inferior margin of the membranous septum.
Point X *Right and Non-coronary Leaflet Commissure*	Location of the commissure between the right and non-coronary leaflets.
Point i *Inferoseptal Recess Roof Midline*	Midline point at the base of the inferoseptal recess roof, in line with the atrial septum. This point is compared to the angle with the non-coronary leaflet nadir to determine the

Variable	Significance
	rotational position of the aortic root relative to the base of the left ventricle.



Supplemental Figure 2. *Calibration plot: observed v predicted probability of PPI. Red dashed line: identity (observed=predicted), blue line and shaded area: Loess fit with 95% CI. HL: Hosmer Lemeshow.*

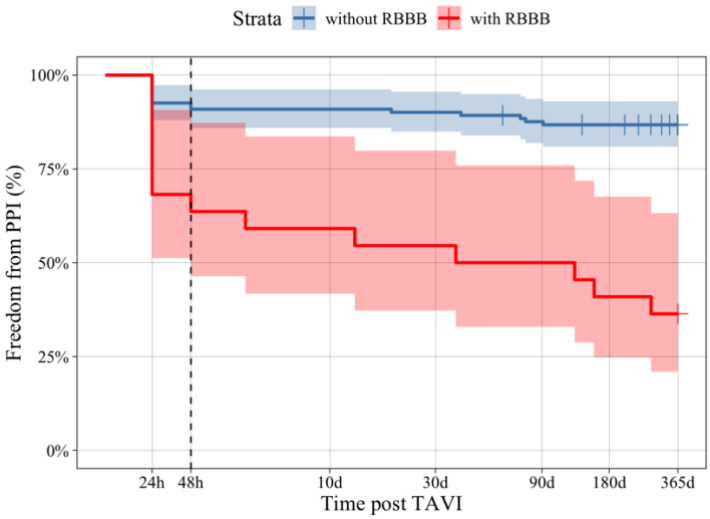
Supplemental Table 3. *K-Fold Cross-Validation and Bootstrap Optimism Correction.*

	Basic model		*Stratified 5-fold cross validation with 10 repeats*		*Optimism-corrected estimates (bootstrap, 10,000 replicates)*	
Calibration Metric	**Value**	**95% CI**	**Value**	**95% CI**	**Value**	**95% CI**
AUC	0.86	[0.77–0.93]	0.84	[0.64–0.97]	0.84	[0.76–0.92]
Brier Score	0.11	–	0.12	[0.07–0.20]	0.12	[0.10–0.16]
Calibration Intercept	0.008	–	-0.045	[-0.875–1.347]	-0.141	[-0.570–0.335]
Calibration Slope	1.060	–	0.944	[0.270–1.777]	0.910	[0.543–1.315]

Supplemental Table 4. *Exhaustive comparison of the final and alternative (competing) models*

	Model Terms	aOR	95% CI	p-value	Brier Score	Calibr. Intercept	Calibr. Slope	AIC	AUC	95% CI	*ROC test p
Final Model	Reference level*	1.00			0.109	0.008	1.06	54.4	0.86	[0.77–0.93]	–
	X-mid B-C angle (per 1º increase)	0.95	[0.91–0.99]	0.0122							
	RBBB pre-TAVI	14.0	[4.56–49.1]	<0.0001							
	†Device depth from Point B measured in *diastole* (per 1mm increase)	1.52	[1.12–2.17]	0.0056							
	†Device depth from Point B measured in *systole* (per 1mm increase)	0.97	[0.81–1.16]	0.7201							
	Oversizing of Self-expanding device (per 1 % increase)	**1.07**	**[1.02–1.13]**	**0.0066**							
	Oversizing of Balloon-expandable device (per 1 % increase)	**1.07**	**[0.88–1.36]**	**0.4900**							
Alternative 1	Reference level*	1.00			0.113	0.0004	1.0386	50.4	0.84	[0.76–0.91]	0.2846
	X-mid B-C angle (per 1º increase)	0.94	[0.90–0.98]	0.0055							
	RBBB pre-TAVI	15.3	[5.13–51.8]	<0.0001							
	†Device depth from Point B measured in *diastole* (per 1mm increase)	1.51	[1.12–2.14]	0.0052							
	†Device depth from Point B measured in *systole* (per 1mm increase)	0.95	[0.80–1.12]	0.5233							
	Self-expanding device	**3.36**	**[1.22–10.4]**	**0.0178**							
Alternative 2	Reference level*	1.00			0.109	-0.0011	1.0396	53.1	0.86	[0.76–0.93]	0.7592
	X-mid B-C angle (per 1º increase)	0.95	[0.91–0.99]	0.0096							
	RBBB pre-TAVI	14.7	[4.83–51.0]	<0.0001							
	†Device depth from Point B measured in *diastole* (per 1mm increase)	1.52	[1.12–2.17]	0.0055							
	†Device depth from Point B measured in *systole* (per 1mm increase)	0.97	[0.81–1.16]	0.7071							
	Oversizing (per 1 % increase)	**1.07**	**[1.02–1.13]**	**0.0039**							
Alternative 3	Reference level*	1.00			0.109	0.0012	1.0528	54.7	0.86	[0.77–0.93]	0.6340
	X-mid B-C angle (per 1º increase)	0.95	[0.91–0.99]	0.0135							
	RBBB pre-TAVI	14.1	[4.69–48.6]	<0.0001							
	†Device depth from Point B measured in *diastole* (per 1mm increase)	1.51	[1.12–2.16]	0.0060							
	†Device depth from Point B measured in *systole* (per 1mm increase)	0.97	[0.81–1.16]	0.7382							
	Self-expanding device	**0.78**	**[0.09–6.08]**	**0.8162**							
	Oversizing (per 1 % increase)	**1.08**	**[0.99–1.19]**	**0.1013**							
Alternative 4	Reference level*	1.00			0.109	0.0072	1.0718	56.0	0.85	[0.77–0.93]	0.9327
	X-mid B-C angle (per 1º increase)	0.95	[0.91–0.99]	0.0139							
	RBBB pre-TAVI	13.9	[4.51–49.18]	<0.0001							
	†Device depth from Point B measured in *diastole* (per 1mm increase)	1.06	[0.87–1.35]	0.5769							
	†Device depth from Point B measured in *systole* (per 1mm increase)	1.51	[1.12–2.15]	0.0059							
	Self-expanding device	**0.97**	**[0.81–1.16]**	**0.7334**							
	Oversizing (per 1 % increase)	**0.69**	**[0.04–10.3]**	**0.7908**							
	Oversizing of Self-expanding device (per 1 % increase)	**1.02**	**[0.78–1.27]**	**0.8719**							

*Model AUC compared to Final Model by a two-sided Bootstrapped test with 5,000 replicates; aOR: adjusted odds ratio; ROC: receiver operator characteristics.
The final model balances predictive performance, parsimony, and clinical interpretability. It includes the predictors consistently associated with PPI, achieves good discrimination and calibration, while avoiding inclusion of poorly predictive or unstable variables. Additionally, self-expanding valves are traditionally oversized significantly more compared to balloon-expandable valves due to their inherent deployment mechanism(213) which is reflected in the final model.

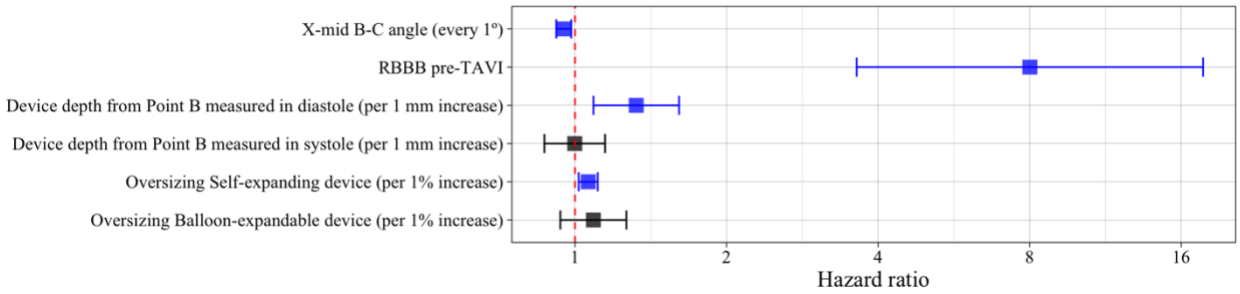


Supplemental Figure 3. *PPI-free survival with and without RBBB pre-TAVI: HR=6.49, (95% CI 3.16–13.4), p<0.0001. Shaded areas: 95% CI.*

Supplemental Table 5. *Cox proportional hazards model predicting post-TAVI PPI requirement over the course of 365 days post-implantation.*

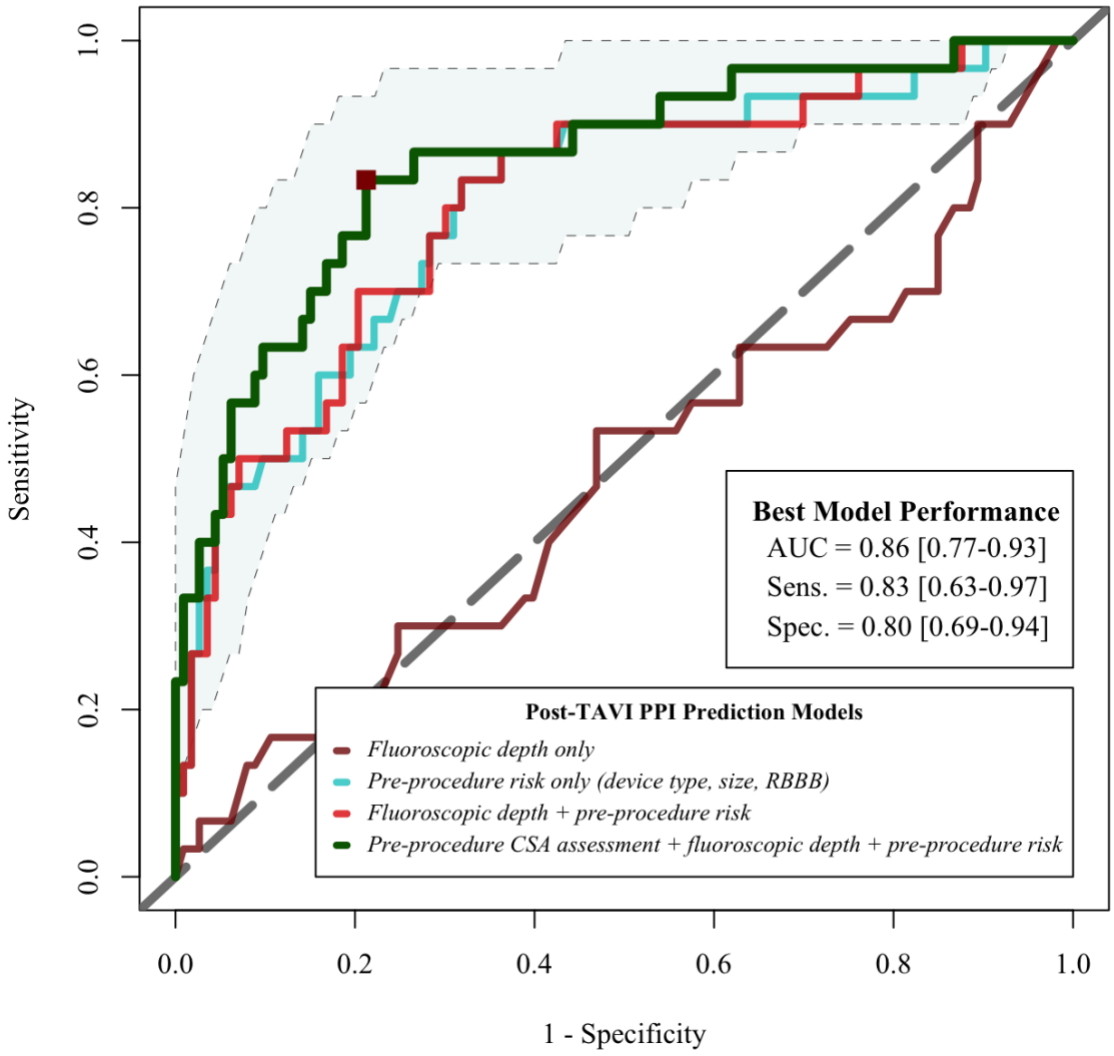
Predictor	**HR**	**95% CI**	***p*-value**
X-mid B-C angle (per 1º increase)	0.95	[0.92–0.98]	0.0030
RBBB pre-TAVI	8.01	[3.63–17.7]	0.0000
†Device depth from Point B measured in *diastole* (per 1mm increase)	1.32	[1.09–1.61]	0.0051
†Device depth from Point B measured in *systole* (per 1mm increase)	1.00	[0.87–1.15]	0.9862
Oversizing of Self-expanding device (per 1 % increase)	1.06	[1.02–1.11]	0.0066
Oversizing of Balloon-expandable device (per 1 % increase)	1.09	[0.94–1.27]	0.2753

†Computed as $H_{computed} = H_{device\ (fluoroscopic)} - H_{point\ measurement\ (CTA)}$



Supplemental Figure 4*. Forest plot: predictors of PPI within 365 days of TAVI.*

CENTRAL ILLUSTRATION



CHAPTER 8: Predicting the Risk of New-Onset Atrial Fibrillation After Transcatheter Aortic Valve Implantation Using Semi-Automated Machine Learning Computed Tomography (CT) Analysis Methods: A Post-Hoc Analysis of CONDUCT-TAVI

This chapter includes work that is currently under peer review.

Presented at:

Cardiac Society of Australia and New Zealand (CSANZ) Annual Scientific Meeting 2025

(Poster Presentation)

Author attribution statement:

I was the lead author involved in the conceptualisation of the study as post-hoc analyses of CONDUCT-TAVI. I assisted with data collection, analysis, cardiac segmentation and manuscript writing.

Initially, this study was proposed as a post-hoc analysis reviewing demographic, electrical, anatomical and procedural predictors of NOAF, which was a secondary outcome from the prospective study detailed in Chapter 6: CONDUCT-TAVI. The study then developed into a detailed volumetric and geometric evaluation of the left atrium using both traditional and machine-learning based methods for measurement. The manuscript includes a locally created mathematically derived algorithm for statistical shape analysis, which was created in collaboration with Dr. Daniel Han and his team at the School of Mathematics and Statistics at the University of New South Wales.

Combining clinical, anatomical, procedural and novel machine learning methods to predict new-onset atrial fibrillation at 1-year after TAVI

Karan Rao[1,2,3], Daniel Han[4], Jonathan Ciofani[1,3], Mohammed Ahmed[3], Jiayi Wen[4], Adelle C.F. Coster[4], Jonathan Ben Daniel[3], Natasha Saad[1], Alexandra Baer[2], Peter Hansen[1,2] & Ravinay Bhindi[1,2,3]

[1] Royal North Shore Hospital, Sydney, Australia

[2] North Shore Private Hospital, Sydney, Australia

[3] University of Sydney, Australia

[4] University of New South Wales

Corresponding author:

Professor Ravinay Bhindi

Royal North Shore Hospital, Reserve Road, St. Leonards, 2065.

Email: ravinay.bhindi@sydney.edu.au

Short Title: Predicting NOAF after TAVI

Word count: 5400 words (excluding abstract and supplementary/appendix).

Funding: This is an investigator initiated and funded project. The implantable loop recorders were provided in kind by BIOTRONIK. Dr. Karan Rao is supported through a National Health and Medical Research Council and Heart Research Australia Postgraduate Scholarship.

Disclosures: The authors have no disclosures or conflicts of interest to report.

Ethics: Northern Sydney Local Health District Ethics Committee

8.1 Abstract

Introduction: New-onset atrial fibrillation (NOAF) is believed to occur in 10–15% of patients within 1 year after transcatheter aortic valve implantation (TAVI) and is associated with increased stroke, rehospitalisation, and mortality. Predictors are poorly defined. We evaluated traditional demographic, anatomical, electrical and procedural risk factors and explored left atrial (LA) segmentation with statistical shape analysis (SSA) using pre-TAVI CT as novel predictors of NOAF.

Methods: We analysed 200 patients with 1-year continuous rhythm monitoring. Multimodality traditional risk factors were evaluated using logistic regression. In the 170 patients with suitable pre-procedural CT, semi-automated LA segmentation was performed, and validated against manual segmentation. SSA was then used to identify geometric differences. A machine-learning classifier (multi-layer perceptron) and Kolmogorov–Smirnov testing assessed shape discrimination.

Results: 31.0% had pre-existing AF; among AF-naïve patients, 21.7% developed NOAF (15.0% of total cohort); 54.0% had no AF (control). Pre-procedural left bundle branch block (OR 2.85, p=0.016) and rapid atrial pacing-induced Mobitz I were associated with NOAF on univariable analysis; pacing-induced Mobitz I remained significant on multivariable analysis (OR 2.75, p=0.021). No other variables were associated with NOAF on logistic regression. Semi-automated segmentation correlated well with manual segmentation. CT-derived LAVi was associated with pre-existing AF (aOR 1.080, p<0.01) but not NOAF (aOR 1.023, p=0.115). SSA detected significant geometric variation between cohorts. The classifier achieved AUC 0.65 (95% CI 0.62–0.67) for separating control and AF shapes.

Conclusions: Patients with NOAF are more likely to have baseline LBBB and pacing induced Mobitz I. Semi-automated LA segmentation is a reproducible tool for atrial geometry assessment. SSA revealed subtle LA shape variations associated with NOAF post-TAVI and serves as a potent target for future work.

8.2 Introduction

Transcatheter aortic valve implantation (TAVI) has revolutionized the management of severe aortic stenosis (AS), providing a minimally invasive alternative to surgical aortic valve replacement (SAVR). New-onset atrial fibrillation (NOAF) remains a frequently encountered complication after TAVI, increasing the post-procedural risk of prolonged hospitalization, stroke, mortality, and permanent pacemaker implantation (PPMI)(73). The reported incidence of NOAF in contemporary randomised control trials varies between 5-10% at 1-year(138, 158), however, these studies have primarily reported clinical AF. Recently, a study utilising Holter monitors found an incidence of 7.0% at 14-days, suggesting an underestimation of subclinical and device-detected NOAF(74).

Prior studies have associated various demographic risk factors for developing NOAF, including advanced age, chronic kidney disease, and peripheral vascular disease(214). Anatomically, left atrial (LA) enlargement, diastolic dysfunction, and concomitant significant mitral regurgitation have been associated with NOAF(214). Procedurally, transapical access may increase the risk of NOAF, although it is now rarely used in contemporary practice(215). Procedural factors such as valve type, degree of prosthesis oversizing, and implantation depth have been well recognized as determinants of atrioventricular block (AVB) but not necessarily for NOAF. Similarly, baseline ECG and invasive electrophysiology (EP) studies have helped to forecast post-TAVI, but their relevance in predicting NOAF has not been well explored.

Additionally, recent advancements in artificial intelligence (AI) and machine learning (ML) have allowed for automated and reproducible cardiac chamber segmentation, potentially enabling more accurate quantification. Beyond this, statistical shape analysis (SSA) is a novel

supplementary technique to detect subtle and preclinical structural changes which may further enhance our arrhythmia risk stratification.

This study systematically examines the periprocedural clinical, anatomical, and electrophysiological associations of NOAF after TAVI. Additionally, it applies semi-automated ML algorithms and novel SSA techniques to routine pre-procedural computed tomography (CT-TAVI) imaging to evaluate the role of LA volume and geometry in patients which develop NOAF after TAVI.

8.3 Methods

This study is a post-hoc analysis of the CONDUCT-TAVI study, and the complete original protocol and methodology have been published previously(180). The primary objective of CONDUCT-TAVI was to evaluate the incidence and predictors of high-grade atrioventricular block (HGAVB) following TAVI, whilst the incidence of NOAF was recorded as a secondary outcome (Chapter 6). Patients with a prior permanent pacemaker, implantable cardioverter-defibrillator (ICD), or previous aortic valve surgery were excluded from the study. Patients were arranged into three groups based on their 1-year follow up: 1) control; 2) NOAF or 3) pre-existing AF.

Anatomical and Electrophysiological Assessments

All participants underwent comprehensive pre-procedural anatomical evaluation, including transthoracic echocardiography (TTE), as well as computed tomography (CT-TAVI) as routine prior to TAVI. The key anatomical variables collected included TTE derived aortic valve area and gradient, left ventricular ejection fraction (LVEF), left atrial (LA) area and presence and quantification of mitral valve disease. Retrospective offline semi-automated

biplane LA strain was performed using available acquisitions in the four-chamber and two-chamber views. From the pre-procedure CT-TAVI, the valve morphology, annular/LVOT measurements, membranous septum length and calcium volumes and distribution were recorded.

All patients underwent pre and post procedure ECG. Targeted invasive electrophysiological studies (EPS) were also conducted immediately before and after TAVI, with measurements including PR interval, QRS duration, atrioventricular (AH) interval, and His-Ventricular (HV) interval. Rapid atrial pacing was performed pre and post-TAVI from 70 beats per minute to 120 beats per minute to assess atrioventricular nodal function, as described by Krishnaswamy *et al.*(69), with the presence of AV Wenckebach (Mobitz type I atrioventricular block) serving as a marker of diseased AV nodal conduction. Patients in complete AVB or atrial fibrillation (or flutter) at the time of the EPS were excluded from rapid atrial pacing manoeuvres. For further details, please see the published protocol(180).

Continuous rhythm monitoring

All patients in the study received either an implantable loop recorder (ILR) (BIOMONITOR III, BIOTRONIK, Berlin, Germany) or if indicated, a permanent pacemaker, which permitted continuous rhythm monitoring over the follow up period (1-year). Data were reviewed daily via CardioMessenger Home Monitoring (BIOTRONIK, Berlin, Germany) by the study team. All arrhythmias were independently verified by a cardiac technologist and electrophysiologist. NOAF was defined as at least 30 seconds of irregular R-R intervals without organized atrial activity. Clinically significant arrhythmias were referred to the treating cardiologist for further management.

Automated cardiac chamber segmentation

All pre-procedural CT-TAVI scans were obtained for offline analysis. The image series corresponding to ventricular end-systole (maximal atrial diastole) was analysed. Patients with inadequately gated CT scans, or incomplete atrial coverage, were excluded from this aspect of the analysis.

To determine the volume and surface area of the LA, the CT files were first imported into 3D Slicer (Version 5.6.2), as shown in Supplementary Figure 1. 3D Slicer(216) is an open-source software freely available for medical image informatics, image processing and 3D visualisation. Prior to full cohort semi-automated segmentation, manual validation was performed on 29 patients. LA architecture and relevant anatomy were manually identified using the segment editor function in cross-sectional, sagittal, and frontal views, excluding pulmonary veins and the LA appendage. A 3D Slicer feature then used Hounsfield units from the CT scan to differentiate tissues and initiate a region-growing process until the entire structure was segmented, followed by further manual fine-tuning.

Semi-automated segmentation was performed using TotalSegmentator AI, which leverages ML algorithms for rapid and consistent segmentation of cardiac chambers. First, the CT files were imported into 3D Slicer, as shown in Supplementary Figure 2. Second, after manually cropping the area of interest, the heart chamber function built into TotalSegmentator AI was used to automatically segment all four chambers (left ventricle, left atrium, right ventricle, right atrium) of the heart and the myocardium. Following manual validation, this technique was used to perform segmentation on the complete cohort.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables are expressed as frequencies and percentages. Comparisons between categorical variables were conducted using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were analysed using the Analysis of Variance (ANOVA) across multiple groups. Logistic regression analysis was performed to evaluate pre-specified associations. Odds ratios (OR) with 95% confidence intervals (CI) were calculated, and statistical significance was defined as $p<0.05$. Variables with a significance value of $p<0.1$ were entered into a multivariable logistic regression model. All statistical analyses were performed using SPSS Version 30.0 (IBM, Armonk, NY).

Statistical Shape Analysis (SSA)

The SSA component of this study was carried out using a novel algorithm pioneered by our research group. To perform SSA of LA geometry, we generated an outer shell mesh of LA points from the automatically segmented cardiac chambers described above. The mitral valve and interatrial septum regions were defined using a distance-based thresholding method. Mitral valve-associated points were those within the top 1% closest to the left ventricle, while septal points were within the top 2% closest to the right atrium. Each LA mesh was centred by subtracting the mean coordinate of all points and scaled using the maximum intra-coordinate distance.

Mathematically, the operations for centring and scaling were performed as follows:

- **Centering:** $x_n^i \leftarrow x_n^i - \frac{1}{N}\sum_{m=1}^{N} x_m^i$, $y_n^i \leftarrow y_n^i - \frac{1}{N}\sum_{m=1}^{N} y_m^i$, $z_n^i \leftarrow z_n^i - \frac{1}{N}\sum_{m=1}^{N} z_m^i$.
- **Scaling:** $x_n^i \leftarrow \frac{x_n^i}{d_{max}}$, $y_n^i \leftarrow \frac{y_n^i}{d_{max}}$, $z_n^i \leftarrow \frac{z_n^i}{d_{max}}$, where

$$d_{max} = \max_{n,m\in[1,N]}\left(\sqrt{\left(x_n^i - x_m^i\right)^2 + \left(y_m^i - y_m^i\right)^2 + \left(z_n^i - z_m^i\right)^2}\right).$$

A reference LA mesh was selected from a randomly chosen patient in the control group, and all other LA meshes were *aligned* to this reference using a Coherent Point Drift (CPD) algorithm, which was applied to anchor points in the mitral valve and atrial septum regions. Once aligned, Cartesian coordinates were converted to spherical polar coordinates, and interpolation was performed using radial basis functions. A *template* shape was generated for each cohort (arranged by AF status) by averaging the radial coordinates of the patients within.

From the 1000 spherical polar angles that were sampled on the surface of each LA after matching (see Supplementary material: Statistical Shape Analysis), we performed non-parametric tests to compare the distribution of radii at each angle for the NOAF, and pre-existing AF groups compared to the control group. The non-parametric tests used were the two sample Kolmogorov-Smirnoff (KS) and the two-sample Cramér-von Mises (CvM) tests. We also calculated the Wassenstein-1 (W1) distance for further quantification of geometric variation.

8.4 Results

Of the 200 patients that were enrolled in CONDUCT-TAVI, a total of 62 (31.0%) patients had a pre-existing history of AF, whilst 30 (15.0% of total cohort, 21.7% of AF naïve cohort) developed new-onset AF (NOAF), and the remaining 108 (54.0%) did not develop AF or have a history of AF (control group).

Baseline Demographics

Table 1 summarizes the baseline characteristics of the study population stratified by AF status. The mean age was comparable among groups ($p = 0.087$). Notably, pre-existing AF patients had a higher proportion of males (80.6%) compared to control (59.3%) and NOAF

(53.3%) (p = 0.007). While BMI and common cardiac risk factors such as hypertension, hypercholesterolemia, diabetes, and coronary artery disease did not significantly differ between groups, peripheral arterial disease, whilst having low prevalence overall, was more common in NOAF patients (16.7%) than control (5.6%) and pre-existing AF (1.6%) (p = 0.017).

On comparison of pre-procedural medications, there was a similar use of beta-blockers and non-dihydropyridine calcium channel blockers between groups (p=0.103), however antiarrhythmic (Class I and III) usage (p<0.001), digoxin usage (p<0.001) and anticoagulation (p<0.001) were more common in the pre-existing AF group, compared to the control group and NOAF. Inversely, aspirin usage was greatest in control (56.5%) and NOAF (56.7%) compared to 16.1% in pre-existing AF (p<0.001).

Imaging and Procedural Characteristics

Imaging characteristics are displayed in Table 2. Pre-procedural echocardiography revealed that pre-existing AF patients had a significantly higher tricuspid regurgitation (TR) velocity (3.05 ± 0.54 m/s) than the NOAF (2.86 ± 0.30 m/s) and control groups (2.61 ± 0.51 m/s) (p < 0.001). LA volume index and LA area were also significantly larger in pre-existing AF (54.02 ± 23.61 mL/m² and 29.87 ± 9.01 cm², respectively) compared to NOAF and control groups (p < 0.001). There was no difference in left atrial strain measurements between NOAF and control groups. Computed tomography (CT) parameters, including valve morphology, membranous septum length, annular and left ventricular outflow tract (LVOT) dimensions, and calcium distribution did not significantly differ across groups. Similarly, procedural characteristics did not vary significantly across groups although patients with pre-existing AF were numerically more likely to require a temporary pacing wire (30.7%) compared to

control (18.5%) and NOAF (13.3%), although this did not reach statistical significance (p=0.09).

Electrophysiological Parameters

Table 3 details electrophysiology characteristics between groups. Pre-TAVI ECG findings demonstrated that first-degree AV block was more common in NOAF (36.7%) when compared to control (27.8%) and pre-existing AF (11.3%) ($p < 0.001$). The HV interval was more prolonged in pre-existing AF (61.7 ± 11.5 ms) compared to control (57.3 ± 10.2 ms) and NOAF (56.7 ± 10.40 ms) ($p = 0.02$). Pre-procedural right atrial pacing was performed in all patients that were not in AF during the EP study, which included all patients in control and NOAF groups, and 38.7% of those with pre-existing AF. On post-TAVI ECG, 2 (6.7%) patients in the NOAF groups were found to be in AF, however no other changes were noted in ECG or EPS derived intervals or change in these intervals.

Clinical Outcomes

There was no difference in all-cause or cardiovascular mortality between groups. There was a proportionately higher rate of cardiovascular rehospitalisation in patients with pre-existing AF (27.4%) compared to NOAF (16.7%) and controls (11.1%), although this did not reach statistical significance. There was a higher proportion of PPMI at 1-year in the pre-existing AF group (30.6%) compared to control (21.3%) and NOAF (20.0%) which also did not reach statistical significance. The incidence of PPMI due to sick sinus syndrome or tachycardia bradycardia syndrome was higher in the pre-existing AF group (8.1%, p=0.12), compared to NOAF (3.3%) and control (0.0%) groups. The incidence of stroke at 1-year did not statistically vary between the groups but was proportionally higher in NOAF (10.0%) and

pre-existing AF (8.1%) groups compared to control (4.6%). There were no differences in major vascular complications or bleeding between groups.

Logistic Regression Analyses

We performed a univariable logistic regression (Table 4) to evaluate risk factors for NOAF at 1-year in previously AF naïve patients. Pre-procedural LBBB [OR 4.12 (1.10-15.34), p=0.035) and pre-procedural rapid atrial pacing induced AV Wenckebach (Mobitz I) were both more associated with NOAF [OR 2.84 (1.22-6.61), p=0016) compared to control. On multivariable regression, pre-procedural rapid atrial pacing induced AV Wenckebach (Mobitz I) remained independently associated. All other demographic, imaging, electrophysiology derived, and procedural characteristics were not associated with incidence of NOAF at 1-year.

Automated Left Atrial Segmentation

Of the 200 patients enrolled in CONDUCT-TAVI, 30 patients had unsuitable CT scans for LA segmentation. 20 (66.7%) were excluded due to inadequate cardiac cycle gating, whilst 10 (33.3%) were excluded due to incomplete LA coverage (Figure 1). Of the 170 that underwent segmentation and analysis, 49 (28.8%) had pre-existing AF, 29 (17.1%) developed NOAF, and 92 (54.1%) had remained AF-free (control) throughout the year of follow-up.

Prior to analysing the dataset using semi-automated segmentation, the process was validated against manual segmentation using the sub-cohort of 29 patients in the NOAF group and showed excellent correlation (Supplementary Figure 3).

On CT analysis (Table 2), patients with pre-existing AF had the largest left atrial volume index (LAVi) at 81.4 ± 34.4 cm^3/m^2, followed by NOAF at 56.8 ± 17.7 cm^3/m^2, and then the control group at 51.5 ± 14.7 cm^3/m^2 (p=0.001). This group also had the largest right atrial volume index (RAVi) at 94.5 ± 52.3 cm^3/m^2, followed by NOAF at 56.3 ± 24.8 cm^3/m^2, and then CONTROL at 49.2 ± 14.5 cm^3/m^2 (p=0.001). Moreover, patients with pre-existing AF had the largest myocardial cell volume index (MCVi) at 84.0 ± 23.3 cm^3/m^2, followed by NOAF at 79.9 ± 23.0 cm^3/m^2, and then control at 72.6 ± 15.1 cm^3/m^2 (p=0.003). There were no differences noted between groups in LA sphericity (%) (p=0.199). On univariable logistic regression (Table 6), there were no differences in LAVi, RAVi or MCVi when comparing NOAF to control. When comparing patients with pre-existing AF to control, LAVi [OR 1.079 (1.050-1.110) p = 0.001], RAVi [OR 1.076 (1.047-1.106) p = 0.001], and MCVi [OR 1.033 (1.013-1.053) p = 0.001], were associated with pre-existing AF compared to control.

Statistical Shape Analysis (SSA)

When comparing NOAF and pre-existing AF LA segmented shapes to the control group, notable differences were identified through SSA. Among the 1000 spherical polar angles sampled across the surface of each LA following shape alignment, the NOAF group demonstrated statistically significant differences in radii distributions at 51 directions using the KS test and at 55 directions using the CvM test ($p < 0.05$). In contrast, the pre-existing AF group showed more extensive differences, with 185 and 245 directions found to be significantly different by the KS and CvM tests, respectively ($p < 0.05$) (Supplementary Figure 4). To further highlight spatial variation, Figure 2 and Supplementary Figures 5A and 5B illustrate the average LA shapes for each group, color-coded by the KS distance, CvM statistic, and 1-Wasserstein (W1) distance. Qualitative assessment of these visual representations revealed that the most pronounced morphological deviations from the control

group occurred at the superior (roof) and lateral walls, with a progressive increase in geometric variation observed from the NOAF to the pre-existing AF groups.

A multi-layer perceptron classifier trained on the 1000-point radii representations of each LA achieved an average area under the receiver operating characteristic curve (AUC) of 0.562 (standard error = 0.001) for distinguishing among the three cohorts, as assessed via 10^4 Monte Carlo simulations. When the NOAF and pre-existing AF groups were combined into a unified "*any"* AF cohort, classification performance showed an average AUC of 0.545 with a standard error of 0.0001 for distinguishing AF from controls.

8.5 Discussion

This retrospective study of 200 TAVI patients with extensive clinical, anatomical and electrophysiology characterisation, and 1-year of continuous rhythm monitoring, reports several key findings. Firstly, we observed a *significant* burden of subclinical device-detected NOAF in the post-TAVI population, with an incidence of 21.7% in the AF naïve population. Secondly, whilst predicting NOAF remains challenging, certain electrical characteristics, such as pre-existing left bundle branch block (LBBB) and rapid atrial pacing induced Mobitz Type 1 may be associated with an increased risk. Lastly, the application of AI-enhanced semi-automated LA segmentation and SSA of routine CT-TAVI, is not only feasible and reproducible, but also shows promise as a novel risk stratification tool for NOAF.

The incidence of NOAF was 21.7% in the AF naïve population (15.0% in the overall population) which is *substantially* higher than in the most recent low-risk PARTNER III (7.0%)(138) and EVOLUT Low Risk(158) (9.8%) trials, although these reported clinical AF, rather than device-detected AF. The specific role of TAVI in directly causing AF remains

uncertain, as older age and AS independently increase myocardial fibrosis resulting in diastolic impairment and atrial enlargement, which are known risk factors for AF. Therefore, whether our findings merely indicate a heightened incidence of device-detected AF in a uniquely high-risk population, or whether electrical and anatomical remodelling post-TAVI directly contribute to the development of NOAF is not entirely clear. A 2015 study which monitored patients for 24 hours prior to their TAVI, detected NOAF in 6.4%, which was associated with a 7-fold increase in 30-day stroke risk(217). This contrasts findings from the LOOP study, which randomised patients with cryptogenic stroke to an ILR, and whilst finding greater detection of subclinical AF, did not conclude any difference in thromboembolism risk at extended follow up(193). Currently, major European and American guidelines continue to recommend anticoagulation for patients with a high thromboembolic risk and device-detected subclinical AF episodes lasting longer than 5 minutes, however management of shorter episodes remains a grey zone(218, 219). Additionally, the NOTION-4 randomised control trial which is currently underway in Europe, will evaluate the potential benefit of 3-months of routine anticoagulation after TAVI, as opposed to antiplatelet therapy alone, and we keenly await the impact on the incidence of stroke and major bleeding(220).

Our logistic regression analyses suggested pre-procedural dynamic assessment of rapid atrial pacing to induce early AV Wenckebach (Mobitz I) was independently associated with the development of NOAF. This protocol was derived from Krishnaswamy *et al.* (2019) where it was demonstrated to be strongly associated with high-grade atrioventricular block and permanent pacemaker requirement at 30-days after TAVI. As a marker of impaired baseline AV nodal conduction, we hypothesize that it may also reflect a more generalised deterioration in the conduction axis. Likewise, the presence of a pre-existing LBBB was also linked to NOAF (OR 4.12, p=0.035) in our cohort. We propose this may be mediated via chronic

ventricular dyssynchrony, which often leads to elevated LA pressures and atrial myopathy(221). These results align with a recently published study evaluating patients with new-onset LBBB monitored with ILRs, which found that 18.8% developed NOAF at 1-year(222). Peripheral arterial disease was more prevalent in the NOAF cohort, however failed to reach statistical significance (OR 3.40, p=0.058), likely a reflection of a relatively small sample size. Notably, all other demographic, anatomical, electrophysiological and procedural risk factors did not predict NOAF.

Our secondary findings helped to gain insights into the key differences between control, NOAF and pre-existing AF groups. Whilst the status (paroxysmal vs. persistent) was not captured in the patients with a pre-existing AF, these patients had higher TR velocity ($p<0.001$), lower LVEF ($p=0.045$) and larger LA volumes ($p<0.001$), an expected outcome of chronic AF induced negative atrial remodelling. Other relevant findings included a male predominance in the pre-existing AF cohort (Pre-existing AF 80.6% versus. control 59.3%, NOAF 53.3%, $p=0.007$), which has been described previously(223). Interestingly, whilst pre-TAVI HV was not different between control (57.29ms) and NOAF (56.73ms) groups, it was significantly longer in the pre-existing AF group (61.68ms, $p = 0.02$) – consistent with our observation that AF may be connected to a global deterioration in conduction pathways.

The presence of AF has previously been described to be a strong adverse prognostic marker, with increased mortality, rehospitalisation, pacemaker and stroke risk(73). However, we did not observe any differences in clinical outcomes in our cohort, although the study was not powered for this purpose.

Semi-automated Chamber Segmentation and Statistical Shape Analysis

We were able to successfully validate and employ semi-automated ML segmentation methods to compare CT-derived chamber volumes across patient groups. Considering it is well known that AF induces bi-atrial cardiomyopathy secondary to structural and electrophysiological remodelling(224), we initially hypothesized that CT-derived volume measurements may be more sensitive and reproducible to identify subtle pre-clinical structural changes in patients that went on to develop NOAF after TAVI. Our null results contradict a recent study by Brahier et al., who report that LAVi ≥ 76 cm^3/m^2 was an independent predictor of NOAF after TAVI [OR=2.54 (1.17-5.53), p=0.019](225). There are many possible causes for the discrepancy; firstly, Brahier *et al.*'s study was a substantially larger cohort (n=1385) compared to 170 patients in our study which were part of a prospective cohort. Secondly, AF detection methods and follow up periods were vastly different, as Brahier *et al.'*s work detected symptomatic AF at 30-days with an incidence of 3.4%, much lower than in our study, and other publications(179). In contrast, our study included subclinical device-detected NOAF up to 1-year, and thus it is plausible that clinically apparent NOAF identified by Brahier *et al.* were associated with more advanced LA myopathy(226) and thus a greater increase in LAVi.

We observed a trend towards MCVi being associated with NOAF [OR 1.024 (0.099-1.049) p = 0.057) which did not quite reach statistical significance. The physiological basis is that mean cell volume may serve as a surrogate marker of left ventricular hypertrophy (LVH) – a product of pressure-induced remodelling commonly associated with severe AS. LVH has been linked to diastolic dysfunction, heart failure with preserved ejection fraction (HFpEF), and left atrial enlargement, forming the substrate for developing AF (227, 228).

We hypothesized that SSA could serve as a sensitive supplementary method for identifying patients at heightened risk of developing NOAF after TAVI by identifying structural variations not appreciated by volume changes alone. Our analysis revealed that the LA roof and lateral wall exhibited the most significant geometric *variation* in patients with NOAF compared to controls, with these alterations becoming more pronounced in patients with known (pre-existing) AF. Our findings partially align with the recent study by Backhaus *et al*. which examined segmented left atria through cardiac magnetic resonance imaging(229). Backhaus *et al.* identified LA roof dilation as an early marker of Heart Failure with Preserved Ejection Fraction (HFpEF) disease progression, preceding global LA enlargement as a predictor of developing AF [OR 1.02 (1.01-1.04), p=0.003](229). Anatomically, the LA roof includes the insertion sites of the pulmonary veins, which are considered the electrical substrate for AF in most patients. Another notable observation was the deterioration in the AUC of our multi-layer perceptron classifier when NOAF and pre-existing AF groups were combined against control. This suggests that NOAF and control groups were *more* alike than the NOAF and pre-existing AF groups. This is perhaps why traditional prediction algorithms have continued to struggle to effectively distinguish NOAF patients from patients without any AF.

Limitations and future directions

This study represents a post-hoc analysis of the CONDUCT-TAVI cohort and is subject to inherent limitations of retrospective analysis. Although patients were prospectively recruited, the original study was powered for high-grade atrioventricular block rather than NOAF and thus excluded individuals with prior aortic valve surgery or cardiac devices. As such, the findings may not be generalisable to all patients undergoing TAVI and should be considered hypothesis-generating.

An additional limitation was the necessary exclusion of 30 patients from the machine learning and statistical shape analysis (SSA) due to suboptimal CT-TAVI imaging. Poor ECG gating impaired accurate atrial measurement, and incomplete scan coverage hindered segmentation. Furthermore, while principal component analysis (PCA) is the conventional SSA method as it enables assessment of shape variation without the need to predefine specific spatial landmarks, when applied to our cohort, it predominantly captured size- and volume-related variation due to the subtle LA shape differences. Future analyses may benefit from volume normalization prior to incorporating PCA to better isolate shape-specific features.

Finally, biplane LA strain was performed retrospectively in patients with control and NOAF. Whilst pre-procedural LA strain is a known prognostic marker post-TAVI(230, 231) and has been associated with NOAF following SAVR(232), the neutral result in this study may be attributed to our small sample size. Future prospective work should incorporate LA strain with focussed imaging (> 40 frames per second), which could be integrated into segmentation and SSA based methods to help refine the prediction of NOAF.

8.6 Conclusion

The results from this study reiterate the notable incidence of NOAF after TAVI and extend our understanding of its predictors. Our findings suggest that specific electrophysiological markers—such as pre-existing left bundle branch block and Mobitz Type 1 induced by rapid atrial pacing—are associated with a higher risk of NOAF within one-year post-TAVI. Furthermore, we successfully demonstrated the use of novel semi-automated ML segmentation techniques and SSA, which were used to reveal subtle geometric differences

with NOAF and pre-existing AF cohorts when compared to those that remained in sinus rhythm.

Future prospective studies can aid in validating these findings, which in turn may help integrate electrophysiological assessments and AI-driven quantification into standard clinical practice – eventually enhancing our risk stratification capacity for NOAF after TAVI.

8.7 Tables and Figures

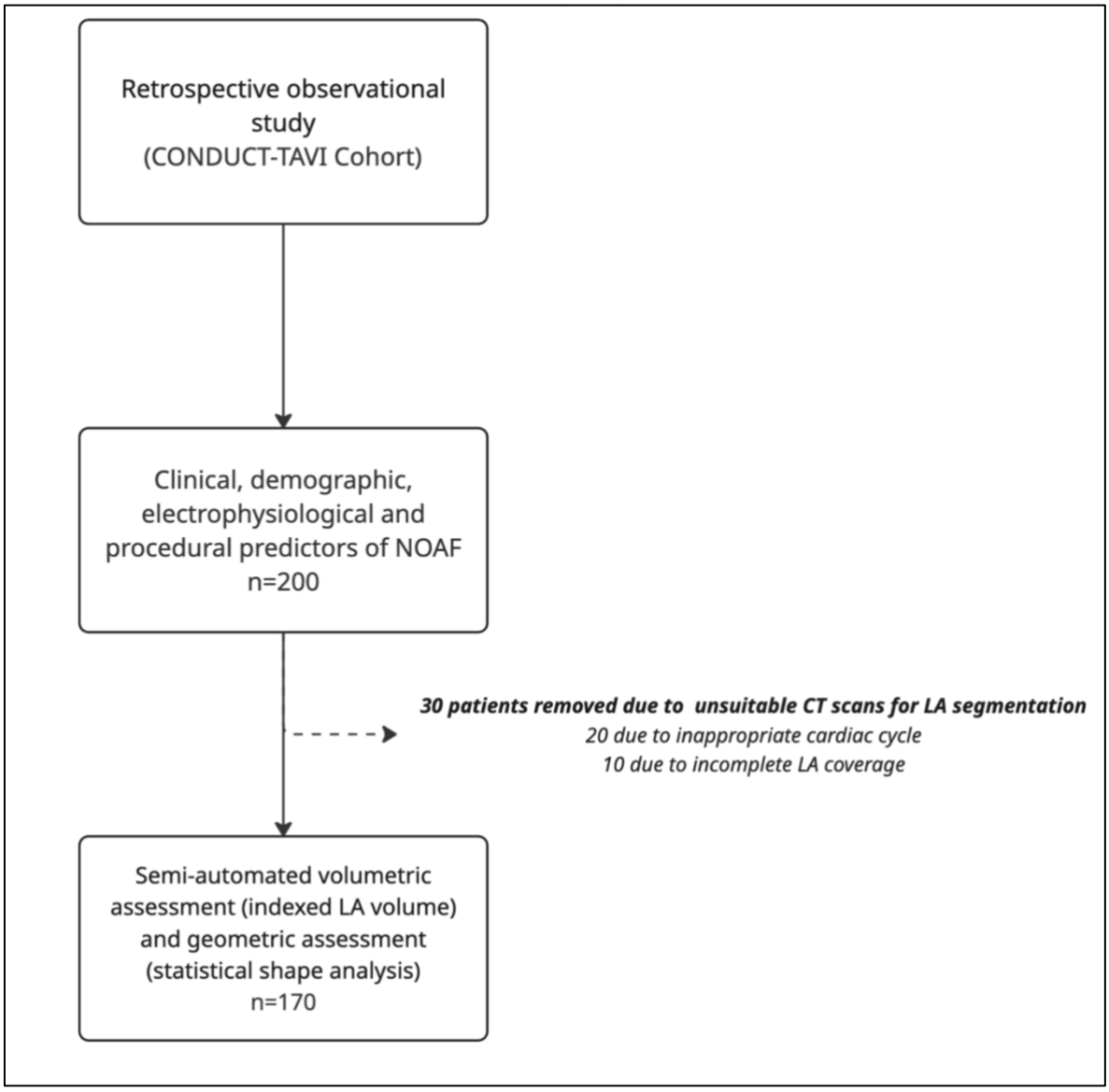


Figure 1: Study flow chart.

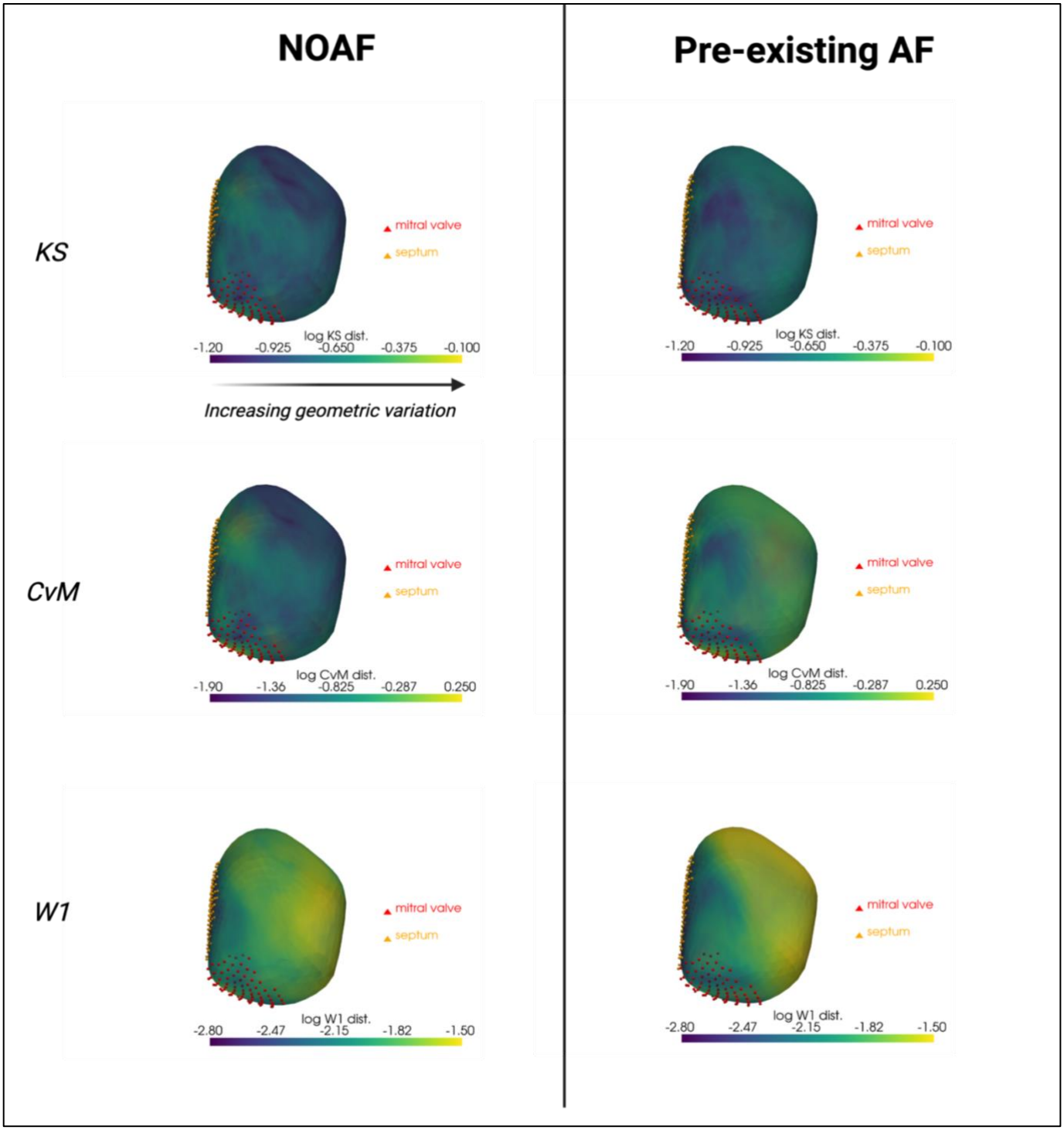


Figure 2: Statistical shape analysis: Plots of the average left atrium shape (NOAF and pre-existing AF) compared to control groups (AF-free), coloured with KS (Kolmogorov-Smirnov) distance, CvM (Cramér–von Mises) statistic and the W1 (1-Wasserstein) distance. The values are shown in logarithmic scale for enhanced visualization, from an anterior perspective with the mitral valve (bottom) and inter-atrial septum (left).

Table 1: Baseline demographics by Atrial Fibrillation (AF) Status

Characteristic	Control (AF-Free) (n=108)	NOAF (n=30)	Pre-existing AF (n=62)	P Value
Age (years)	81.53 ± 6.52	81.43 ± 6.23	83.65 ± 5.91	0.087
Gender (male)	64 (59.3)	16 (53.3)	50 (80.6)	0.007**
BMI (kg/m²)	28.08 ± 5.66	27.04 ± 5.83	26.87 ± 4.53	0.323
Hypertension	93 (86.1)	24 (80.0)	46 (74.2)	0.152
Hypercholesterolemia	69 (63.9)	21 (70.0)	30 (48.4)	0.067
Diabetes	30 (27.8)	8 (26.7)	17 (27.4)	0.993
Coronary Artery Disease	38 (35.2)	8 (26.7)	24 (38.7)	0.524
Peripheral Arterial Disease	6 (5.6)	5 (16.7)	1 (1.6)	0.017**
Previous Stroke	7 (6.5)	2 (6.7)	8 (12.9)	0.326
Chronic Obstructive Pulmonary Disease	16 (14.8)	2 (6.7)	3 (4.8)	0.094
Chronic Kidney Disease	27 (25.0)	10 (33.3)	19 (30.6)	0.571
STS/ACC TAVR Risk Score ()	3.31 ± 2.28	3.36 ± 3.15	3.24 ± 2.15	0.974
Frailty Score/Index	4.05 ± 0.81	4.13 ± 0.63	4.24 ± 0.55	0.298
Admission medications				
B blocker or non-DHP CCB	40 (37.0)	9 (30.0)	36 (58.1)	0.103
Anti-arrhythmic (Class I or III)	2 (1.9)	0 (0.0)	10 (16.1)	<0.001
Digoxin	0 (0.0)	0 (0.0)	11 (17.7)	<0.001
Anticoagulation Warfarin Direct oral anticoagulant	5 (4.6) 1 (0.9) 4 (3.7)	0 (0.0) 0 (0.0) 0 (0.0)	49 (79.1) 5 (8.1) 44 (71.0)	<0.001
Aspirin	61 (56.5)	17 (56.7)	10 (16.1)	<0.001

Table 2: Imaging and procedural characteristics by AF status

Characteristic	Control (AF-Free) (n=108)	NOAF (n=30)	Pre-existing AF (n=62)	P Value
Pre-Procedural echocardiography				
Septal Thickness (cm)	1.24 ± 1.08	1.15 ± 0.20	1.12 ± 0.18	0.617
Left Ventricular Hypertrophy	62 (59.0)	16 (53.3)	33 (55.9)	0.832
AV Mean Gradient (mmHg)	45.78 ± 15.25	47.17 ± 12.88	40.61 ± 18.40	0.078
AVA (Continuity) (cm²)	0.79 ± 0.28	0.82 ± 0.26	0.81 ± 0.27	0.850
AVA (Indexed) (cm²/m²)	0.44 ± 0.20	0.42 ± 0.11	0.42 ± 0.13	0.714
TR velocity (m/s)	2.61 ± 0.51	2.86 ± 0.30	3.05 ± 0.54	**<0.001**
Left Ventricular Ejection Fraction (%)	60.05 ± 8.58	58.50 ± 6.71	56.46 ± 10.27	0.045

Mitral Regurgitation None Trivial or mild >Mild	 14 (13.2) 77 (71.3) 17 (15.7)	 0 (0.0) 25 (83.3) 5 (16.7)	 4 (6.6) 44 (71.0) 14 (22.6)	0.215
LA Volume Indexed Pre (mL/m²)	39.41 ± 14.72	43.76 ± 12.31	54.02 ± 23.61	**<0.001**
LA Area Pre (cm²)	23.59 ± 6.27	24.35 ± 4.92	29.87 ± 9.01	**<0.001**
LA strain Reservoir Conduit Contractile	 21.20 (IQR 7.62) -9.70 (IQR 4.65) -10.98 (IQR 4.90)	 21.63 (IQR 11.14) -8.78 (IQR 5.45) -13.80 (IQR 7.63)	 N/A N/A N/A	 0.575 0.582 0.107
Pre-procedure CT				
Cusps				0.084
Tricuspid Bicuspid	98 (90.7) 10 (9.3)	26 (86.7) 4 (13.4)	62 (100.0) 0 (0.0)	
Membranous Septal Length (mm)	2.64 ±2.27	2.58±1.43	3.27±2.61	0.208
Annular Perimeter (mm)	77.43±8.50	77.80±8.05	80.28±7.44	0.084
Annular Area (mm³)	466.65±102.93	472.02±105.73	499.82±92.10	0.112
LVOT Perimeter (mm)	76.28±9.37	75.79±8.66	79.00±8.66	0.123
LVOT Area (mm²)	443.94±114.64	441.20±106.41	476.12±106.61	0.157
Annular/LVOT Area Ratio	1.06±0.10	1.08±0.09	1.06±0.11	0.808
Total Overall Leaflet Calcification (mm³)	1006.53±673.18	921.30±476.47	1057.37±821.51	0.681
Total DLZ Calcification (mm³)	832.21±540.49	772.00±396.61	928.11±730.84	0.419
Total LVOT Calcium Volume (mm³)	48.31±92.34	36.40±68.49	61.90±106.28	0.441
Procedural characteristics				
Valve Type				0.564
Balloon-Expandable	44 (40.7)	9 (30.0)	24 (38.7)	
Self-Expanding	64 (59.3)	21 (70.0)	38 (61.3)	
Valve Size (mm)				0.172
20 23 26 29 34	2 14 42 30 20	2 3 7 12 6	0 7 16 20 19	
True Oversizing (%)	15.34±9.43	14.85±9.24	16.32±8.92	0.719
Pre or post dilatation	27(25.0)	6 (20.0)	11 (17.7)	0.470
Implantation Depth (mm)	3.44±2.01	3.31±2.02	3.99 (1.91)	0.186

Membranous Septal Length - Implantation Depth (mm)	-0.62±2.86	-0.85±2.38	-1.05±3.45	0.706
Temporary pacing wire at end of case	20 (18.5)	4 (13.3)	19 (30.7)	0.090

Table 3: Electrophysiological Parameters by AF Status

Parameter	Control (AF-Free) (n=108)	NOAF (n=30)	Pre-existing AF (n=62)	P Value
Pre-TAVI ECG				
Sinus Rhythm Atrial Fibrillation Atrial Flutter 1st Degree AV Block 2nd Degree AV Block Complete AV Block Paced	78 (72.2) 0 (0.0) 0 (0.0) 30 (27.8) 0 (0.0) 0 (0.0) 0 (0.0)	19 (63.3) 0 (0.0) 0 (0.0) 11 (36.7) 0 (0.0) 0 (0.0) 0 (0.0)	18 (29.0) 33 (53.2) 4 (6.5) 7 (11.3) 0 (0.0) 0 (0.0) 0 (0.0)	**<0.001**
Heart Rate (bpm)	70.66 ± 12.20	71.43 ± 10.81	72.24 ± 13.92	0.729
PR Interval (ms)	181.98 ± 32.49	188.73 ± 34.44	187.48 ± 34.76	0.528
AH Interval (ms) Pre-TAVI	108.52 ± 33.23	116.40 ± 41.41	106.17 ± 31.14	0.474
HV Interval (ms) Pre-TAVI	57.29 ± 10.16	56.73 ± 10.40	61.68 ± 11.50	**0.022**
QRS Interval (ms)	100.85 ± 26.40	100.87 ± 27.28	99.37 ± 25.50	0.934
Intraventricular Conduction Abnormalities				0.211
RBBB LBBB	20 (18.7) 5 (4.7)	2 (6.7) 5 (16.7)	9 (14.5) 2 (3.2)	
Right Atrial Pacing Performed?	108 (100.0)	30 (100.0)	24 (38.7)	**<0.001**
Mobitz Type I Induced by Right Atrial Pacing?	25 (23.6)	14 (46.7)	7 (29.2)	0.048**
Post-TAVI ECG				
Sinus Rhythm Atrial Fibrillation Atrial Flutter 1st degree AV block 2nd Degree AV block Complete AV block Paced Other (Junctional)	50 (46.7) 1 (0.9) 0 (0.0) 40 (37.0) 0 (0.0) 2 (1.9) 10 (9.3) 4 (3.7)	12 (40.0) 2 (6.7) 1 (3.3) 14 (46.7) 0 (0.0) 1 (3.3) 0 (0.0) 0 (0.0)	9 (14.5) 30 (48.4) 2 (3.2) 10 (16.1) 0 (0.0) 4 (6.5) 6 (9.7) 1 (1.6)	**<0.001**
Heart Rate (bpm)	76.65 ± 13.56	78.77 ± 9.81	73.52 ± 16.13	0.188
PR Interval (ms)	198.19 ± 36.15	207.26 ± 39.26	200.58 ± 43.31	0.550

AH Interval (ms)	114.05 ± 32.82	114.30 ± 40.02	109.21 ± 35.59	0.850
HV Interval (ms)	65.99 ± 11.96	65.17 ± 11.04	69.61 ± 14.90	0.196
QRS Interval (ms)	126.78 ± 26.06	133.38 ± 27.17	127.33 ± 29.77	0.513
Intraventricular Conduction Abnormalities				0.260
RBBB LBBB	15 (13.9) 50 (51.5)	2 (6.7) 20 (66.7)	9 (16.7) 25 (46.3)	
Right atrial pacing performed?	91 (84.3)	27 (93.1)	19 (30.6)	**<0.001**
Mobitz Type 1 Induced by Right Atrial Pacing?	26 (28.6)	10 (37.0)	4 (21.0)	0.489
ΔHV (ms)	8.76 ± 10.01	9.17 ± 8.92	8.41 ± 8.71	0.061
ΔAH (ms)	5.14 ± 22.78	0.26 ± 17.29	7.21 ± 16.11	0.474

Table 4: Logistic regression evaluating risk factors for developing NOAF at 1-year in AF naïve patients

Variable	**Odds Ratio (95% CI) NOAF vs. control (n=138) *excluding persistent AF (n=62)**	**P Value**	**Adjusted Odds Ratio (95% CI) NOAF vs. control (n=138) *excluding persistent AF (n=62)**	**P Value**
Demographics				
Age	0.99 (0.94-1.06)	0.943		
Gender	1.27 (0.56-2.87)	0.561		
BMI	0.97 (0.90-1.04)	0.376		
Hypertension	0.64 (2.26-1.84)	0.412		
Hypercholesterolaemia	1.32 (0.55-3.16)	0.535		
Diabetes	0.95 (0.38-2.35)	0.904		
CAD	0.67 (0.27-1.65)	0.383		
PAD	3.40 (0.96-12.05)	0.058		
Prior Stroke	1.03 (0.20-5.24)	0.971		
COPD	0.41 (0.09-1.90)	0.254		
CKD	1.50 (0.63-3.60)	0.364		
STS Score	1.01 (0.85-1.19)	0.935		
Imaging measurements				
Echo-derived				
Aortic valve Mean gradient	1.01 (0.98-1.03)	0.649		
Aortic valve area (continuity)	1.42 (0.34-5.87)	0.632		
LA volume (indexed)	1.02 (0.99-1.06)	0.224		
LA area	1.02 (0.95-1.10)	0.563		
Septal Thickness	0.82 (0.32-2.08)	0.669		

LVH	0.79 (0.35-1.80)	0.577		
LVEF	0.98 (0.93-1.03)	0.364		
TR velocity	3.02 (0.75-12.14)	0.120		
MR > mild	1.07 (0.36-3.19)	0.902		
Post procedural PVL > mild	0.57 (0.12-2.71)	0.481		
CT-derived				
Calcium volume at device landing zone	1.00 (0.99-1.01)	0.569		
Membranous septum length	0.99 (0.81-1.21)	0.896		
ECG and EPS derived measurements				
Pre-PR	1.01 (0.99-1.02)	0.320		
Post-PR	1.01 (1.00-1.02)	0.264		
Pre-QRS	1.00 (0.99-1.02)	0.998		
Post-QRS	1.01 (0.99-1.03)	0.238		
Pre-AH	1.01 (0.99-1.02)	0.281		
Post-AH	1.00 (0.99-1.01)	0.973		
Pre HV	0.99 (0.96-1.04)	0.791		
Post HV	0.99 (0.96-1.03)	0.743		
RAP induced AVW pre	2.84 (1.22-6.61)	**0.016**	2.75 (1.16-6.51)	0.021
RAP induced AVW post	1.47 (0.60-3.63)	0.403		
Pre RBBB	0.31 (0.07-1.43)	0.134		
Pre LBBB	4.12 (1.10-15.34)	**0.035**	3.81 (0.99-14.76)	0.053
Procedural measurements				
Self-expanding valves	1.60 (0.67-3.83)	0.287		
Oversizing Percentage (%)	0.99 (0.95-1.04)	0.796		
Implantation depth	0.97 (0.79-1.19)	0.762		

Table 5: 1-year Clinical Outcomes based on AF Status

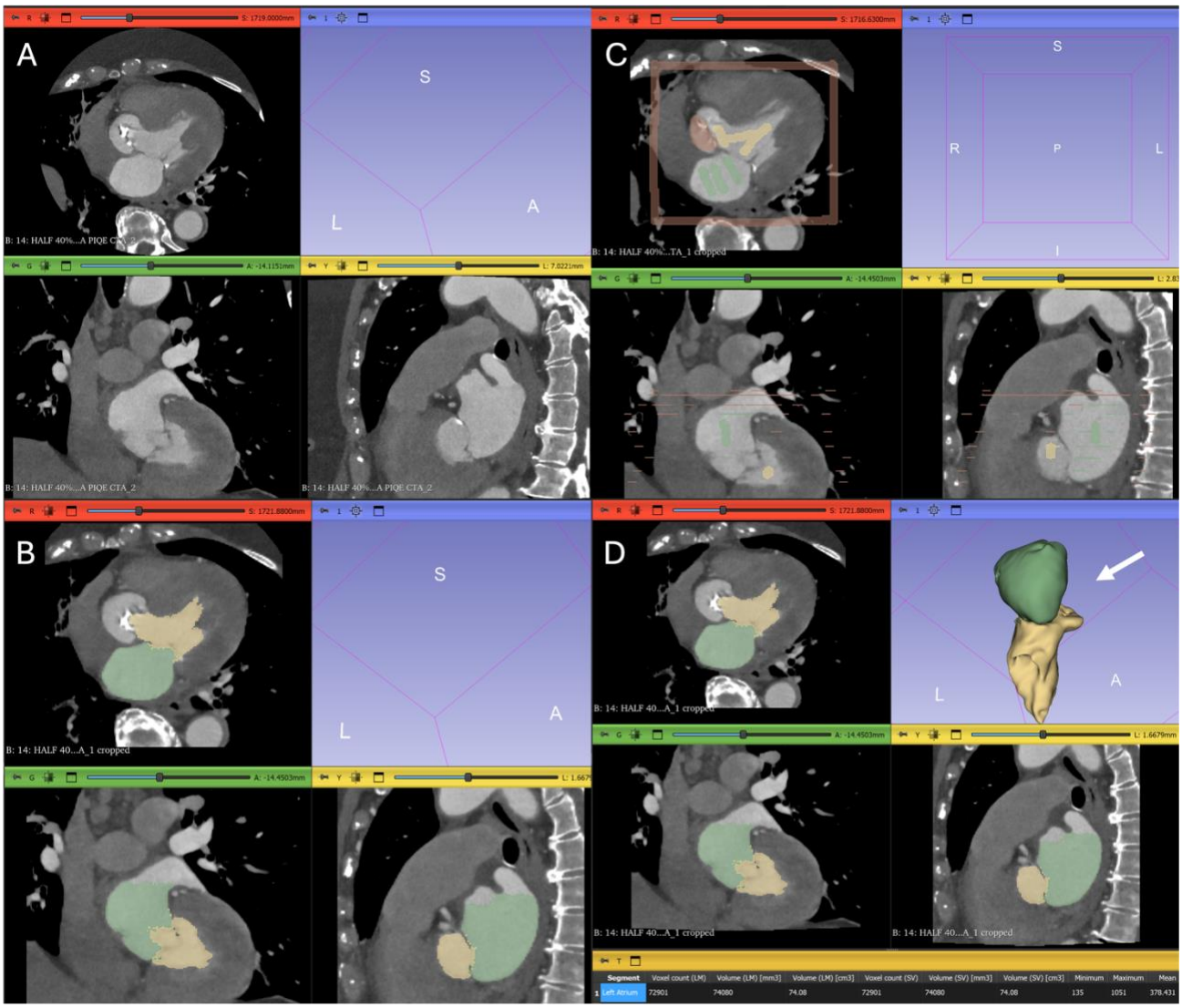
Parameter	Control (AF-Free) (n=108)	NOAF (n=30)	Pre-existing AF (n=62)	P Value
Mortality				
- All Cause	10 (9.3)	1 (3.3)	4 (6.4)	0.525
- Cardiovascular	2 (1.9)	1 (3.3)	2 (3.2)	
- Non-cardiovascular	8 (7.4)	0 (0.0)	2 (3.2)	
Hospitalisation				0.232
- Cardiovascular	12 (11.1)	5 (16.7)	17 (27.4)	
- Non-cardiovascular	15 (13.9)	5 (16.7)	6 (9.7)	
Any new PPMI	23 (21.3)	6 (20.0)	19 (30.6)	0.333
PPMI due to HGAVB 1 year	23 (21.3)	5 (16.7)	14 (22.6)	0.803
PPMI first 48 hours	14 (13.0)	3 (10.0)	10 (16.1)	0.702
PPMI due to SSS or Tachy-Brady syndrome	0 (0.0)	1 (3.3)	5 (8.1)	0.012
Stroke	5 (4.6)	3 (10.0)	5 (8.1)	0.459

Major vascular complication or bleeding	4 (3.7)	2 (6.7)	2 (3.2)	0.640

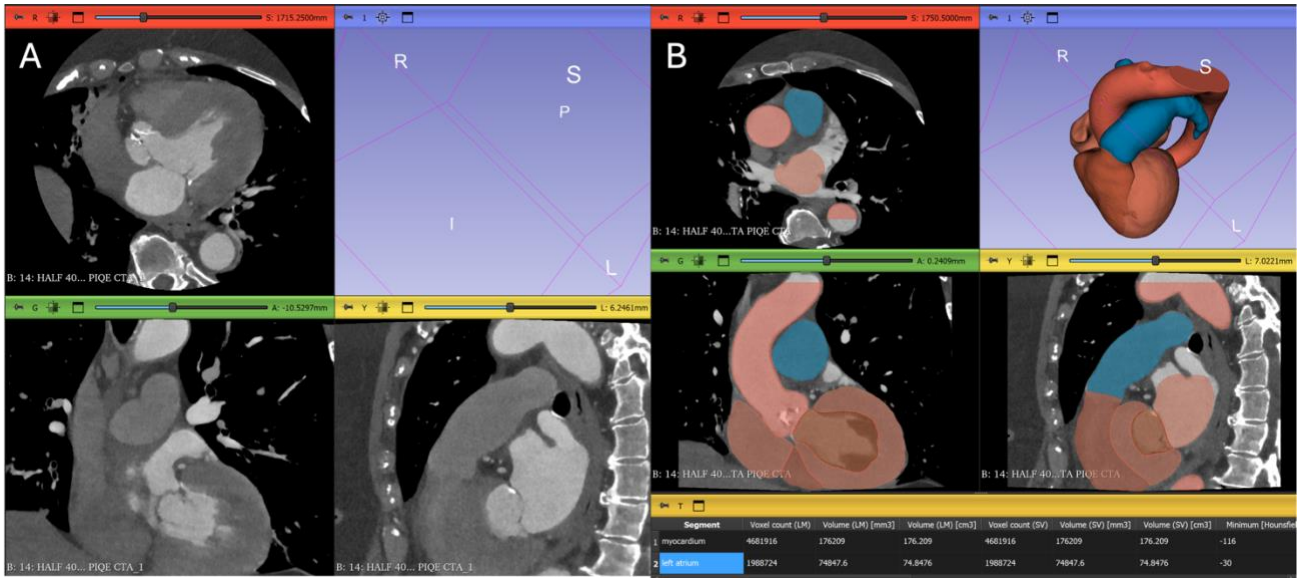
Table 6: Univariable logistic regression of CT derived left atrial volume indexed (LAVi), right atrial volume indexed (RAVi) and mean cell volume indexed (MCVi) compared between new-onset AF and sinus rhythm (control) groups, and pre-existing AF and control groups.

Univariable Logistic Regression				
	NOAF vs. Control (AF-free)		**Pre-existing AF vs. Control (AF-free)**	
	Odds Ratio [95% CI]	**p Value**	**Odds Ratio [95% CI]**	**p Value**
LAVi [cm^3/m^2]	1.022 [0.995 - 1.050]	*0.114*	*1.079 [1.050 – 1.110]*	**0.001**
RAVi [cm^3/m^2]	1.022 [0.998 - 1.046]	0.075	1.076 [1.047 – 1.106]	**0.001**
MCVi [cm^3/m^2]	1.024 [0.999 - 1.049]	0.057	1.033 [1.013 – 1.053]	**0.001**

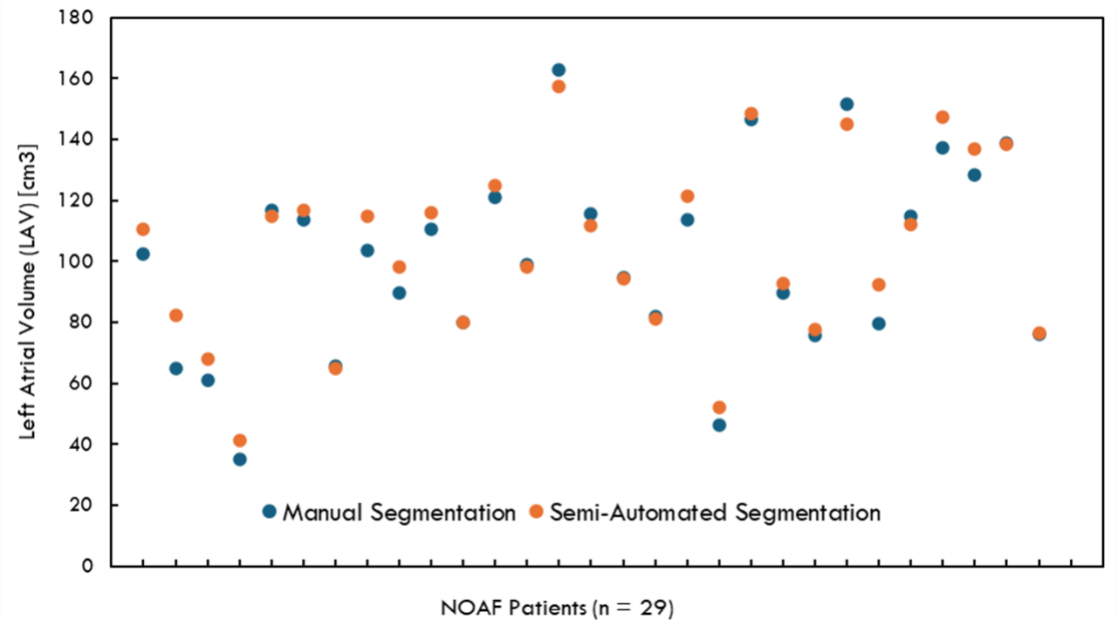
8.8 Appendix



Supplementary Figure 1: Image Analysis using Manual Segmentation. A: Step-1 (Manual segmentation) – An example of CT file imported into 3D Slicer. B: Step-2 (Manual segmentation) – Manual identification of regions of interest (left atrium) excluding pulmonary veins and left atrial appendage. C: Step-3 (Manual segmentation) – Region growing and propagation using Hounsfield units, paying careful attention to exclude pulmonary veins. D: Step-4 (Manual segmentation) – Interactive fine-tuning to refine the segmentation by adding or removing anatomical locations and rerunning the algorithm



Supplementary Figure 2*:* Image Analysis using Semi-Automated Machine Learning Methods *A: Step-1 (Semi-automated segmentation) – An example of CT file imported into TotalSegmentator B: Step-2 (Semi-automated segmentation) – Built-in heart chamber function in TotalSegmentator AI used to segment all four chambers of the heart and the myocardium*



	Manual Segmentation	Semi-automated Segmentation	p Value
LAV [cm^3]	100.56 ± 31.47	104.04 ± 29.85	0.668

Supplementary Figure 3: *Scatter plot showing a comparison of left atrial volume (LAV) and Left Atrial Surface Area (LAsA) obtained using manual and semi-automated segmentation methods for NOAF patients. Table shows comparison of the mean LAV and LAsA between two methods, with no evidence of statistically significant differences.*

Shape analysis

From the automatically segmented chambers of the heart, the outer shell mesh of points for the left atrium (LA) was made for each patient. We chose a reference LA from a randomly selected patient and then match the (target) LAs for all patients in the no AF (control) group. To aid in orientation, we identified the mitral valve and inter-atrial septum regions on each LA mesh by thresholding the set of 3D coordinate points based on distance away from other heart chambers. We used $\boldsymbol{x^i}$ to denote the vector of coordinates containing N mesh points for the i[th] patient. The coordinates on the LA mesh associated with the mitral valve, $\boldsymbol{x^{i,MV}}$, was defined as the points whose distance to the closest point on the left ventricle was within the top 1% of points. The coordinates on the LA mesh associated with the septum, $\boldsymbol{x^{i,S}}$, was defined as the points whose distance to the closest point on the right atria was within the top 2% of points. Then, every LA mesh was centred by subtracting the mean 3D coordinate of all outer mesh points and scaled using the maximum intra-coordinate distance. If (x_n^i, y_n^i, z_n^i) is the vector of the n[th] 3D coordinate of the i[th] patients LA, then the operations to centre the coordinates of the LA mesh are:

$x_n^i \leftarrow x_n^i - \frac{1}{N}\sum_{m=1}^{N} x_m^i$, $y_n^i \leftarrow y_n^i - \frac{1}{N}\sum_{m=1}^{N} y_m^i$, $z_n^i \leftarrow z_n^i - \frac{1}{N}\sum_{m=1}^{N} z_m^i$.

The operation to scale the coordinates of the LA mesh are: $x_n^i \leftarrow \frac{x_n^i}{d_{max}}$, $y_n^i \leftarrow \frac{y_n^i}{d_{max}}$, $z_n^i \leftarrow \frac{z_n^i}{d_{max}}$,

where $d_{max} = \max_{n,m\in[1,N]} \left(\sqrt{\left(x_n^i - x_m^i\right)^2 + \left(y_m^i - y_m^i\right)^2 + \left(z_n^i - z_m^i\right)^2} \right)$.

To match the centered and scaled LA meshes between the reference and targets, we used the Coherent Point Drift (CPD) algorithm for rigid point set registration on the set of "anchor" points in the mitral valve and septum regions, $\boldsymbol{x^{i,MV}}$ and $\boldsymbol{x^{i,S}}$ [**Myronenko2010**]. Once the target LA mesh coordinates were matched to the reference LA, the coordinates were then converted to spherical polar coordinates, $\left(x_n^i, y_n^i, z_n^i\right) \rightarrow (r_n^i, \theta_n^i, \phi_n^i)$, and the set of coordinates were interpolated using radial basis functions via the standard Python

scipy.interpolate package. The new interpolated points of the LA mesh, $(\rho_s^i, \vartheta_s, \varphi_s)$, were chosen such that (ϑ_s, φ_s) were angles generated from the Fibonacci lattice with $s = 1,2,\cdots,S$ and $S = 10^3$ points. The values of ρ_s^i were obtained from the radial basis function interpolations of $\left(r_n^i, \theta_n^i, \phi_n^i\right)$ at the polar angles (ϑ_s, φ_s). Given that (ϑ_s, φ_s) are spherical polar angle coordinates that are shared between every no AF patient LA mesh, we can create a set of average template shape coordinates, $(\rho_s, \vartheta_s, \varphi_s)$, where $\rho_s = \frac{1}{P}\sum_{i=1}^{P} \rho_s^i$ with P being the number of no AF patients.

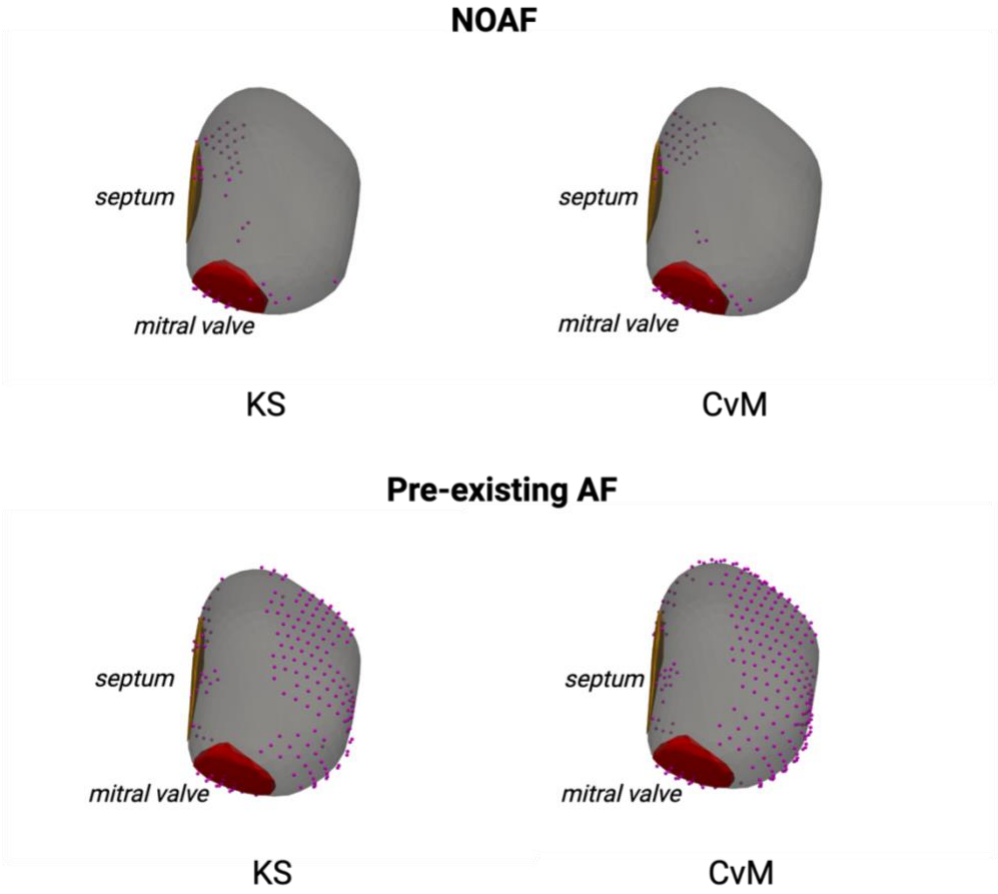
The procedure of matching two different co-ordinate points can be summarized as follows:

1. Obtain outer shell mesh points
2. Define mitral valve and septum regions using thresholding
3. Center and scale mesh points
4. Choose a reference mesh through random sampling
5. Match every mesh to the reference mesh using the CPD algorithm
6. Interpolate every mesh to a set of spherical polar coordinates $(\rho_s^i, \vartheta_s, \varphi_s)$ where (ϑ_s, φ_s) are angles generated from the Fibonacci lattice.

Using the same procedure as above, we then matched each of the LA meshes in the NOAF and pre-existing AF groups. These meshes were matched using the average template shape of the no AF group, $(\rho_s, \vartheta_s, \varphi_s)$. Doing so yielded a set of radial coordinates, $\boldsymbol{\rho}^{nAF} \in \mathbb{R}^{P_{nAF} \times S}$, $\boldsymbol{\rho}^{NOAF} \in \mathbb{R}^{P_{NOAF} \times S}$ and $\boldsymbol{\rho}^{pAF} \in \mathbb{R}^{P_{pAF} \times S}$, corresponding to the groups no AF, new-onset AF and pre-existing AF, respectively. The number of patients in each group is denoted by P_{nAF}, P_{NOAF} and P_{pAF}. To detect differences in shape, we performed two-sample Kolmogorov-Smirnov (KS) tests along each polar direction, (ϑ_s, φ_s) for $\boldsymbol{\rho}^{NOAF}$ against $\boldsymbol{\rho}^{nAF}$ and $\boldsymbol{\rho}^{pAF}$ against $\boldsymbol{\rho}^{nAF}$. These tests provide a KS test statistic and a two-tailed p-value for each polar direction that determined whether the distribution of radii observed from the NOAF or pre-

existing AF groups were significantly different to the distribution of radii observed from the no AF group. Using these tests, significantly different regions of the LA could be identified between the two disease groups and the control group.

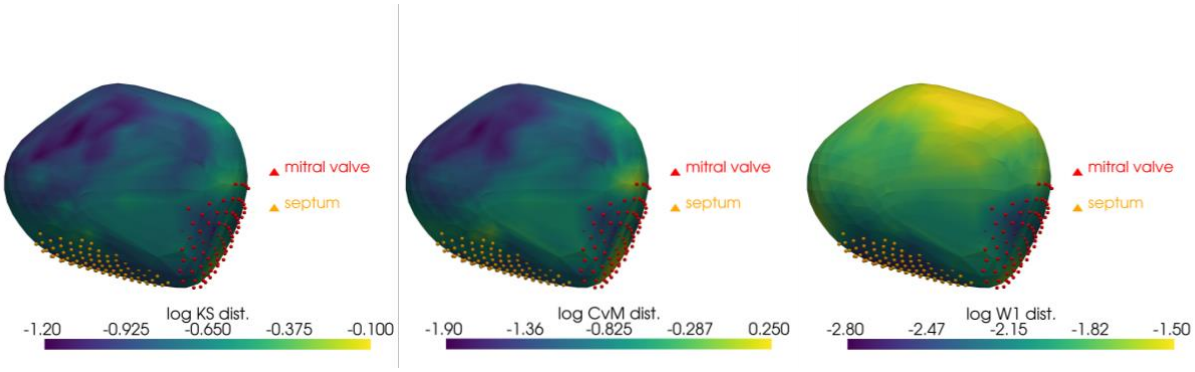
[**Myronenko2010**] Myronenko, A. and Song, X., 2010. Point set registration: Coherent point drift. *IEEE transactions on pattern analysis and machine intelligence*, *32*(12), pp.2262-2275.



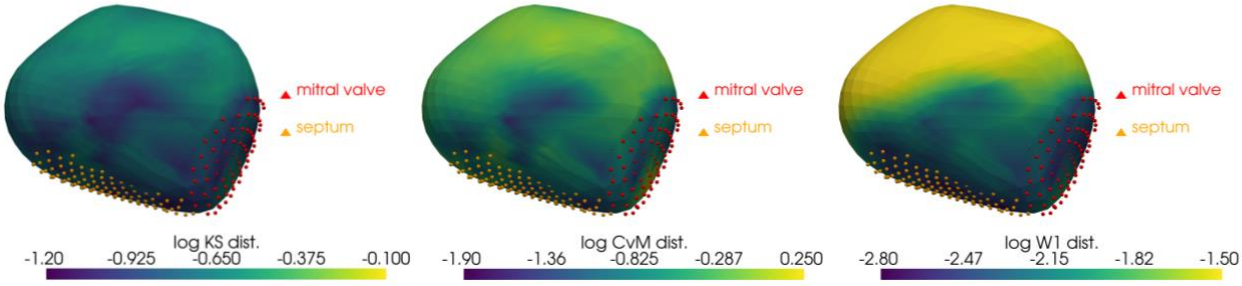
Supplementary Figure 4: Schematic LA diagrams to represent significant points of difference (purple dots) in the NOAF (top) and pre-existing AF (bottom) groups compared to control (AF-free), arranged by the Kolmogorov-Smirnov (KS) test (left side) and the Cramer-von Mises (CvM) test (right). LA orientated using the mitral valve (red) and septum (black).

Supplementary Figure 5A: *Plots of the* average left atrium shape (NOAF and pre-existing AF compared to control patients, coloured with KS distance, CvM statistic and the 1-Wasserstein distance (W1). The values are shown in logarithmic scale for enhanced visualization. From a right anterior oblique view showing the septum on the lower left and mitral valve in the lower right.

NOAF

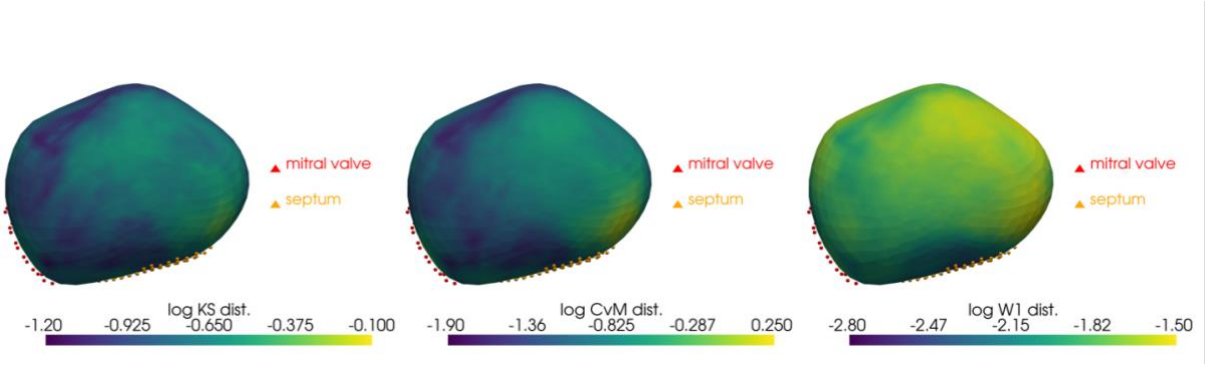


Pre-existing AF



Supplementary Figure 5B: *From a posterior view of the LA with the septum (right) and mitral valve (left)*

NOAF



Pre-existing AF

CHAPTER 9: The association of aortic stenosis with the cardiac conduction system, a combined observational and Mendelian randomization study

Currently under peer review.

Presented at:

1. PCR Tokyo Valves Conference (2024)
2. Cardiac Society of Australia and New Zealand Annual Scientific Meeting (2025)

Author contribution statement:

This chapter has been submitted for publication and remains under peer review. It includes work for which I am co-first author (along with Dr. Jonathan Ciofani). Along with Dr. Ciofani, I co-conceived and co-designed the study concept. I collected, analysed and interpreted the clinical aspects of the data, whilst Dr. Ciofani was primarily involved in the Mendelian randomization analyses. I led the drafting and finalisation of the manuscript. The other co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

The influence of calcific aortic stenosis on atrioventricular conduction: insights from CONDUCT-TAVI and Mendelian randomization analyses

*Karan Rao[a,b,j] MD MPH, *Jonathan L Ciofani[a,b,c] MD MPH, Daniel Han[d,e,f] PhD, Milad Nazarzadeh[g,h] DPhil, Kazem Rahimi[g,h,I] PhD, Alexandra Baer[j] BSN MSHM, Natasha Saad[a], Princess Neila Litkouhi[a,b] MD BMed, Usaid Allahwala[a,b,j] MBBS PhD, Peter Hansen[a,j] MBBS, PhD, Ravinay Bhindi[a,b,j] MBBS, PhD

(a) Department of Cardiology, Royal North Shore Hospital, Sydney, Australia
(b) Sydney Medical School, The University of Sydney, Sydney, Australia
(c) Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK
(d) Medical Research Council Laboratory of Molecular Biology, Cambridge, UK
(e) Department of Physiology, Development and Neuroscience, University of Cambridge, UK
(f) School of Mathematics and Statistics, University of New South Wales, Sydney, Australia
(g) Deep Medicine, Oxford Martin School, University of Oxford, Oxford, UK
(h) Nuffield Department of Women's and Reproductive Health, Medical Science Division, University of Oxford, Oxford, UK
(i) National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
(j) Department of Cardiology, North Shore Private Hospital, Sydney, Australia

*Karan Rao and Jonathan L Ciofani are joint first authors

Short Title: Influence of calcific AS on atrioventricular conduction

Correspondence to:

Professor Ravinay Bhindi
Department of Cardiology, Royal North Shore Hospital
Reserve Road, St Leonards 2065
Australia
Email: ravinay.bhindi@sydney.edu.au

9.1 Abstract

Background

Aortic stenosis (AS) may prolong atrioventricular (AV) conduction secondary to calcium infiltration of the atrioventricular-His-pathway, which is hypothesized to contribute to bradyarrhythmia and sudden cardiac death in this cohort.

Objectives

This study investigates the correlation between calcific AS and impaired AV conduction.

Methods

We performed an observational study and Mendelian randomization (MR) analyses. The observational study was a sub-analysis on AS patients undergoing transcatheter aortic valve implantation (2021-2023). Regression analyses were used to assess the association between aortic valve calcium volumes with markers of AV conduction derived from electrophysiology studies. The primary MR analyses used European-ancestry genome-wide association studies for AS (653,867 participants including 13,765 cases), PR interval (271,570 participants) and AV block (291,645 participants including 5,536 cases). The exposure outcome was the genetic liability for AS, whilst the outcome was prolonged PR interval or AV block.

Results

The mean age in the observational study (n=196) was 81.8 years, 64.8% were men, and 46(23.6%) had first-degree heart block. There was no significant association between total aortic valve complex calcium volume and first-degree heart block; PR, AH or HV intervals; or AV Wenckebach cycle length. On MR, no association was found between genetic liability for AS and PR interval (beta -0.41, 95%CI -1.33-0.51, p=0.38). Additional analyses evaluating genetic liability for AS and AV block suggested a possibly significant association

on IVW analysis (OR 1.15, 95%CI 1.02-1.30, p=0.02), but this was not supported by sensitivity analyses.

Conclusions

This study found no meaningful association between distribution of aortic valve calcification and PR, AH or HV interval. Separately, on MR analyses, there was no association between the genetic liability of AS, and atrioventricular conduction. These findings may challenge the hypothesis that calcific AS impairs baseline atrioventricular conduction.

9.2 Introduction

Aortic stenosis (AS) is the most common valve pathology affecting 12.4% of the population over the age of 75 years(233). It is typically degenerative, involving fibro-calcific remodelling of the aortic valve complex resulting in leaflet restriction. When AS is severe and untreated, it can have a mortality up to 50% at 5 years, with an incidence of 9.2% for unexplained sudden cardiac death(234). Reduced cardiac output, progressive myocardial fibrosis and ischaemia, as well as abnormal atrioventricular (AV) conduction(235) have been proposed as contributors to mortality.

Abnormal atrioventricular conduction has been hypothesized to be driven by left ventricular hypertrophy or calcium extension into the interventricular septum. The AV-His-Purkinje pathway lies near to the aortic valve complex (AVC). Specifically, the His bundle traverses and bifurcates at the membranous interventricular septum which is located within the interleaflet triangle between the non and right coronary (aortic) cusps. In cases of severe AS, it is hypothesized that valvular calcification could extend into the neighbouring conduction pathway, potentially disrupting AV nodal conduction. This association has been explored previously in small-scale historical studies, where a correlation between calcific AS and

delays in PR interval, His bundle, and interventricular conduction has been observed(12, 13, 235). However, there is a paucity of data involving detailed assessment of calcium volume distribution in the aortic valve apparatus and its association with atrioventricular conduction. Furthermore, complete atrioventricular block is commonly observed after transcatheter aortic valve implantation, and it is not clear as to whether patients with severe calcific aortic stenosis have pre-existing conduction disease with reduced reserve, or whether the atrioventricular block is purely secondary to the implanted valve.

This study aims to investigate the association of calcific AS with AV conduction through an observational study and Mendelian randomization (MR) method. The observational study aims to study patients with known AS and correlate the imaging derived volume and distribution of aortic valve calcium with invasively measured markers of AV conduction. The MR methodology allows investigation of potentially causal relationship between an exposure variable (AS) and outcome variable (atrioventricular conduction delay). MR relies on the premise that genetic polymorphisms contribute to an individual's phenotype and the random inheritance of these phenotype-determining genetic polymorphisms is analogous to assignment to a treatment group in a randomised control trial(236), thus aiming to mitigate reverse causation and confounding. This approach has previously been used to demonstrate potentially causal associations between risk factors and cardiovascular diseases including coronary disease and AS(237, 238), as well as between common cardiovascular risk factors and AV block(239).

9.3 Methods

Observational Study

Study Design

This study included 196 patients with symptomatic severe AS from November 2021 until October 2023, and performed a sub-analysis on data which was prospectively collected from an active clinical study on patients awaiting transcatheter aortic valve implantation (TAVI)(180) (CONDUCT TAVI: ACTRN1261001700820) at a large tertiary referral hospital in Sydney, Australia. Those with a pre-existing permanent pacemaker or prior aortic valve surgery were excluded. The study was approved by Northern Sydney Local Health District Ethics Committee.

Computed Tomography (CT) Analysis

All patients underwent multi-detector CT angiography. Image acquisition and sequences were per standard pre-TAVI protocols and not mandated by the study. Images were analysed offline, using 3Mensio medical imaging software (Pie Medical Imaging, Netherlands).

Volumetric calcium analyses of the aortic valve complex using pre-specified variables was performed. The primary analysis was performed on the aortic valve complex (AVC), which was defined as the combination of the basal leaflets (first 10mm from annular plane to aortic root), and the upper LVOT (from annular plane to 5mm into LVOT) (Figure 1). Multiple secondary analyses were performed on differential calcium volumes split by location (LVOT) as well as by aortic cusps (non-coronary cusp, left coronary cusp and right coronary cusp) (Figure 1). The Hounsfield (HU) unit threshold for calcium detection was manually adjusted for each scan to ensure accurate and comprehensive capture of calcification.

12 Lead ECG and Electrophysiology Study

Atrioventricular conduction was assessed using non-invasive 12-lead ECG and targeted invasive electrophysiology testing. ECG derived PR and QRS intervals were recorded, along with the overall rhythm and presence of interventricular conduction disease.

Targeted electrophysiology studies (EPS) were performed immediately prior to the planned TAVI using a mobile electrophysiology system (BIOTRONIK, Berlin, Germany). A standard quad-polar non-deflectable electrophysiology catheter (BIOTRONIK, Berlin, Germany) was inserted using ultra-sound guided transfemoral venous access. The Atrial-His (AH) and His-Ventricular (HV) signals were documented by positioning the catheter in the lower right atrium (RA), and the His signal was identified as the intervening spike between the atrial and ventricular signal. The AH interval was recorded from the onset of the atrial signal to the onset of the His bundle signal on the His catheter recording. The HV interval was recorded from the onset of the His signal on the His catheter, to the earliest ventricular (QRS) signal on the concurrent 12 lead ECG. The intervals were logged once reproducible (+/- 2ms over at least 3 beats). Finally, rapid atrial pacing was conducted to test the AV Wenckebach cycle length as per the original study (CONDUCT-TAVI) protocol. Pacing commenced at 10 beats above the patient's heart rate (or 70 beats per minute, whichever was higher) and was performed in 20 beat salvos and increased by 10 beats per minute until 120 beats per minute, or if the patient's AV node became refractory (AV Wenckebach cycle length).

Notably, as these measurements were recorded prior to the TAVI procedure, all patients were under conscious sedation during the time of the study.

Statistical analysis

Statistical analyses were performed using SPSS Version 29 (IBM, United States). The primary independent variable was total AVC calcium volume (mm^3) whilst secondary variables included pre-defined calcium parameters divided by location within the AVC (non-coronary cusp, right coronary cusp, left coronary cusp and left ventricular outflow tract). The association between predictors and categorical outcome variables was assessed using logistic regression; association with continuous outcome variables was assessed using multiple linear regression with adjustment for confounders. A significance threshold of $p < 0.05$ was used.

Mendelian randomisation

Study Design and Data Sources

The present study was extended using two-sample Mendelian randomisation (MR) analyses. For the main analysis, the exposure variable was genetic liability for aortic stenosis, and the outcome was PR interval. Both exposure and outcome data were sourced from European ancestry populations since population homogeneity is a requirement for the samples used in a two-sample MR analysis. Three further core assumptions of MR are that the genetic variants should be: (i) strongly associated with the exposure; (ii) exclusively associated with the outcome via the exposure; and (iii) independent of potential confounders. To address the first criterion, uncorrelated genetic variants were selected that were significantly associated with the exposure at $p<5x10^{-8}$; and to account for the latter two criteria, sensitivity analyses were performed as described below.

Data for the present study are publicly available. Ethical approval and consent were obtained by the original studies. Datasets were selected predominantly based on large sample size and data availability for analysis. The exposure AS dataset was extracted from a genome wide association study (GWAS) meta-analysis of 10 cohorts which included 653,867 European

participants (13,765 AS cases)(240). As a sensitivity analysis, MR calculations were performed using a restricted subset of five SNPs that were also shown to be associated with aortic valve calcification ($p<0.05$) based on computed tomography assessment of 6,942 European participants(240). The outcome PR interval data was from a GWAS meta-analysis of 40 cohorts including 271,570 European ancestry participants(241). As a positive control, outcome data for heart failure was also extracted from a European GWAS meta-analysis of 486,160 participants overall, including 14,262 cases(242). The present study was then extended by analysing the relationship between genetically predicted liability for AS and AV block, as determined by International Classification of Diseases codes in the FinnGen cohort (5,536 cases and 286,109 controls)(243). Detailed case definitions for each study are available from the original articles (Supplementary Table 7).

Single-nucleotide polymorphisms (SNPs) that were associated with the exposure variable at $p<5x10^{-8}$ were extracted. Linkage disequilibrium clumping was performed ($r^2 < 0.001$, 10 Mb distance cut-off) and the variants with the smallest p-values were selected for further analysis. Palindromic SNPs were excluded. F-statistics were calculated and only SNPs with values >10 were retained for analysis.

Mendelian Randomisation Statistical Analyses

The primary MR analysis was an inverse variance weighted (IVW) random-effects meta-analysis of the Wald ratios for each genetic variant. Results are expressed as a beta value for genetically predicted change in PR interval duration (ms) per unit increase in log odds of genetic liability to AS. To evaluate for violation of the main MR assumptions, we conducted sensitivity analyses including weighted-median, weighted-mode, MR-Egger, MR-PRESSO and outlier exclusion by Cook's. Leave-one-out analyses were also performed for potential

outliers. Since each method has different assumptions, concordance between methods provides confidence in the conclusion. Weighted-median assumes at least half the instrumental variables are valid. Weighted-mode assumes the most common causal effect is consistent with the true effect. MR-Egger uses the Instrument Strength Independent of Direct Effect assumption, requiring that the strength of pleiotropic effects from the genetic variants to the outcome are independent of the association strength between variants and exposure. The average pleiotropic effect of the genetic variants is estimated by the MR-Egger intercept. MR-PRESSO revises the estimate after outlier removal(244). An alternative method of outlier identification was by Cook's distance, with subsequent IVW analysis following outlier exclusion. Cochran's Q-statistic tests for genetic variant heterogeneity. As a further sensitivity analysis, the primary and aforementioned sensitivity MR analyses were performed using a more liberal p-value cut-off for SNP inclusion of $p<5x10^{-6}$.

Statistical analyses were performed using R version 1.4.1106 with the TwoSampleMR package. Preparation of this manuscript was based on the STROBE-MR Guidelines(245).

9.4 Results

Cross-sectional observational cohort study

From November 2021 until October 2023, 196 patients with severe AS were included in the study. The overall demographics are displayed in Table 1. The mean age was 81.8 years (+/- 6.3), and 64.8% of participants were men. The median STS-PROM mortality risk score (%) was 2.78 (IQR 2.99) corresponding to low surgical risk. There was a history of atrial fibrillation in 61 (31.1%) patients, whilst 72 (36.7%) were on a beta blocker, and 12 (6.1%) were on a non-dihydropyridine calcium channel blocker at the time of ECG and EPS. The

median of the mean aortic valve gradient was 42.0mmHg (IQR 15.0), whilst the median echocardiography (volume time integral) derived aortic valve area was 0.80 cm^2 (IQR 0.29).

Table 1 also specifies the ECG and EPS details of the cohort. On 12 Lead ECG analysis, 113 (57.9%) were in sinus rhythm, whilst 36 (18.5%) were in atrial fibrillation or flutter. 46 (23.6%) patients were found to be in first degree atrioventricular block, defined as a PR interval greater than 200 milliseconds (ms), whilst no patients had a *high-grade* atrioventricular block (HGAVB), defined as Mobitz II or complete heart block. The mean PR interval was 183.5ms (±33.1), and mean QRS interval was 100.2ms (±26.3). Right bundle branch block was present in 30 (15.3%) patients, whilst left bundle branch block was present in 12 (6.1%) patients.

When comparing patients with sinus rhythm to those with first degree AV block (Table 2), the age (81.2±6.9 vs. 83.0±4.9 years, respectively p = 0.11) and proportion of males (59.6 vs. 67.4%, respectively p = 0.36) were similar across both groups of patients. On echocardiography, the aortic valve mean gradient was lower in patients with first degree AV block (41.13 vs 48.07mmHg respectively, OR 0.96 [0.93-0.99], p = 0.01). There was no difference when comparing other echocardiographic characteristics including septal thickness, aortic valve area and left ventricular ejection fraction (LVEF). There was no difference between groups when comparing beta blocker or non-dihydropyridine calcium channel blocker usage (Table 2). Similarly, there was no difference between groups when comparing pre-defined CT derived calcium variables.

On multiple linear regression, there was no relationship between the primary outcome of total AVC calcium volume and PR, AH and HV intervals or rapid atrial pacing (AV Wenckebach), when adjusted for age, gender and aortic valve mean gradient (Table 3).

Mendelian randomisation study

In the primary IVW analysis, there was no evidence of a significant association between genetically predicted liability of AS and PR interval (beta: -0.41, 95% CI -1.33-0.51, p = 0.38; Figure 2). This was consistent on all sensitivity analyses including weighted median (beta: -0.08, 95% CI -0.57-0.42, p = 0.76), weighted mode (beta: -0.19, 95% CI -0.78-0.39, p = 0.53), and MR-Egger (beta: 0.86, 95% CI -1.52-3.24, p = 0.49). MR-Egger intercept was non-significant (Supplementary Table 1). There was significant heterogeneity identified by Cochran's Q statistic (Q statistic: 124.92, $p < 0.0001$); nevertheless, similar neutral results were obtained after exclusion of outliers by both MR-PRESSO (beta: -0.24, 95% CI -0.80-0.33, p = 0.43) and Cook's distance (IVW beta: -0.17, 95% CI -0.98-0.64, p = 0.68; Supplementary Table 2). Leave-one-out analyses are presented in Supplementary Figure 2, accompanied by scatter and funnel plots presented in Supplementary Figures 2 and 3, respectively. The more liberal SNP inclusion criteria of $p < 5 \times 10^{-6}$ led to an increase in the number of included SNPs from 16 to 56, yet the MR analysis results were similarly neutral (Supplementary Table 3). Further sensitivity analyses using a restricted subset of 5 SNPs that were additionally associated with aortic valve calcification based on computed tomography also yielded neutral results (Supplementary Table 5). The positive control analysis demonstrated expected results. A significant association was identified between genetically predicted liability of AS and heart failure (IVW odds ratio (OR) 1.16, 95% CI 1.09-1.24, $p < 0.0001$), with this positive result supported by all sensitivity analyses (Supplementary Table 4). On further evaluation of the relationship between genetically predicted AS and AV block,

a significant association was identified on IVW analysis (OR 1.15, 95% CI 1.02-1.30, p=0.02), but this was not supported by the sensitivity analyses weighted-mode (OR 1.21, 95% CI 0.97-1.50, p=0.11), weighted-median (OR 1.15, 95% CI 1.00-1.33, p=0.052) nor MR-Egger (OR 1.13, 95% CI 0.79-1.61, p=0.52) (Supplementary Table 6).

9.5 Discussion

The present study used two complementary methodological approaches to evaluate the relationship between calcific aortic stenosis and AV conduction. The results demonstrate no evidence that the presence of AVC calcification is associated with prolongation of AV conduction. The observational study found no significant relationship between pre-defined calcium variables and first-degree heart block. Similarly, there were no clinically relevant associations between total AVC calcium volume and markers of atrioventricular conduction including PR, AH and HV duration. Concordantly on MR analyses, there was no significant association between genetically predicted liability for calcific AS and PR interval, and the association between genetically predicted AS and AV block was not robust to sensitivity analyses.

Despite a neutral result for the relationship between calcific AS and AV conduction disturbance, a substantial burden of bradyarrhythmia has previously been reported in patients with symptomatic severe AS. In a previous analysis of 40 patients with severe AS and syncope, AV block was the identified aetiology of syncope in 35%(246), and in a prospective study of 106 severe AS patients investigated with one week of continuous ECG monitoring, 5.8% were identified to have HGAVB(247), with similar findings in a study of 435 TAVI candidates undergoing 24-hour pre-procedural ECG monitoring(184). One of the leading hypotheses for this has traditionally been disruption of the conduction system by fibrosis and

calcium deposition. This hypothesis has been further supported by evidence that disruption of the AVC by TAVI(248) and encroachment in the context of peri-annular complications of infective endocarditis(249) similarly lead to conduction system disease.

Additionally some historical studies have supported the role of calcification specifically, including an analysis of 24 AS patients where 12 patients with aortic valve calcification had significantly longer HV intervals than 12 patients without calcification(12). However other studies have demonstrated discordant findings. One analysis of 22 patients with syncope and AS found no association between aortic valve calcification and HV interval(235). Similarly, Asmarats *et al*. showed no statistically significant association between increased Agatston calcium score and increased arrhythmic events in their study of 106 patients, albeit this analysis was not restricted to bradyarrhythmia(247). The present study is a larger cohort that benefits from contemporary CT resolution with volumetric calcium characterisation and detailed invasive EPS data. Despite this, the current analysis similarly found no significant association between AVC calcium volume and PR, AH, or HV intervals. This was supported by the MR analyses which similarly demonstrated a neutral result for the relationship between genetically predicted liability for AS and PR interval, with concordant findings on sensitivity analyses including a restricted analysis using only SNPs which were associated with aortic valve calcification. While the association between genetically predicted AS liability and AV block was statistically significant on IVW analysis, the results of the weighted-mode, weighted-median and MR-Egger analyses were all non-significant and thus the IVW analysis should be interpreted with caution. The null results on sensitivity analyses may be explained by horizontal pleiotropic effects and inclusion of invalid instruments in the IVW analysis that were excluded in the sensitivity analyses. Together, these results suggest that calcific AS may not have a causal role in AV conduction disease.

Similarly, the results did not support the hypothesis that asymmetric calcium deposition, particularly in the NCC and RCC regions, which are in closer anatomical proximity to the bundle of His, may predispose to prolonged AV node conduction due to localised infiltration. A possible explanation may be a fibrotic-predominant AS phenotype causing conduction disease, in lieu of calcium deposits. Although difficult to obtain, histopathological or cardiac magnetic resonance imaging data would better clarify the underlying mechanisms of this finding.

The main strength of the present study is the multimethodological approach, including a cohort of patients with prospective characterisation of CT and EPS data, paired with complementary MR analyses. Nevertheless, there are still several limitations to consider for both the prospective cohort and MR studies. In the observational arm, there was no control (non-AS) group available with dedicated CT and EPS data for comparison, and therefore future prospective studies should prioritise inclusion of a control arm. Given that the MR study concordantly demonstrated an overall neutral result, it was consequently important to include a positive MR control, which expectedly demonstrated clear evidence for a positive causal relationship between genetic liability for AS and heart failure, consistent with previous reports(250, 251). It is important to note that all patients received sedation for the EP study which may have increased vagal tone, and approximately a third of patients used AV node blocking agents (beta blocker or non-dihydropyridine calcium channel blocker) at baseline. The PR, AH intervals and rapid atrial pacing to determine AV Wenckebach cycle length are particularly prone to fluctuations in the autonomic nervous system, and it is possible that any potentially significant association was dampened by these medications. However, the HV interval is considered a more robust and reliable component of AV conduction and is also

assessable in patients with atrial fibrillation, unlike the PR and AH interval. The assessment of AV conduction could be made more robust with the use of a provocative testing via a procainamide challenge during decremental atrial pacing to further stress the atrioventricular node.

There are additional limitations unique to the MR analysis. Specifically, the inclusion criteria for the AS exposure dataset were not strictly limited to severe AS, and so inclusion of mild and moderate AS cases may have diluted a true positive association. However, despite this the positive control analysis was noted to demonstrate a robust association between genetically predicted liability for AS and heart failure. Additionally, the primary MR analysis was not restricted to strictly calcific AS, since some proportion of cases may have been a non-calcific phenotype. The majority of patients with AS do demonstrate a calcific phenotype, but nevertheless this limitation was formally addressed by performing supplementary analyses using SNPs that, in addition to being significant for AS at the conventional threshold of $p<5x10^{-8}$, were also associated with valvular calcification at $p<0.05$ as per the original analysis(240). The present analysis used a two-sample MR approach with overlapping samples, most notably with overlap from UK Biobank and deCODE for the analysis between AS and PR interval. However the impact of this overlap is unlikely to be of practical significance for two reasons: first, only strong instrumental variables with F-statistic >10 were used, and it has previously been shown that overlapping samples is a more substantial issue in the context of weak instrument bias(252); and secondly, bias due to sample overlap in two-sample MR increases the risk of false positive results, whereas the present study reports an overall neutral relationship.

9.6 Conclusions

The present combined analyses did not support the hypothesis that AVC calcification increases the risk of AV nodal conduction disease. This result challenges the belief that local aortic valve calcification infiltrates and disrupts the conduction pathway in patients with AS. This is important in both shaping our understanding of conduction disease pathogenesis in the context of AS and should inform future work focused on predicting and reducing the risk of conduction disease after valvular intervention.

9.7 Figures and Tables

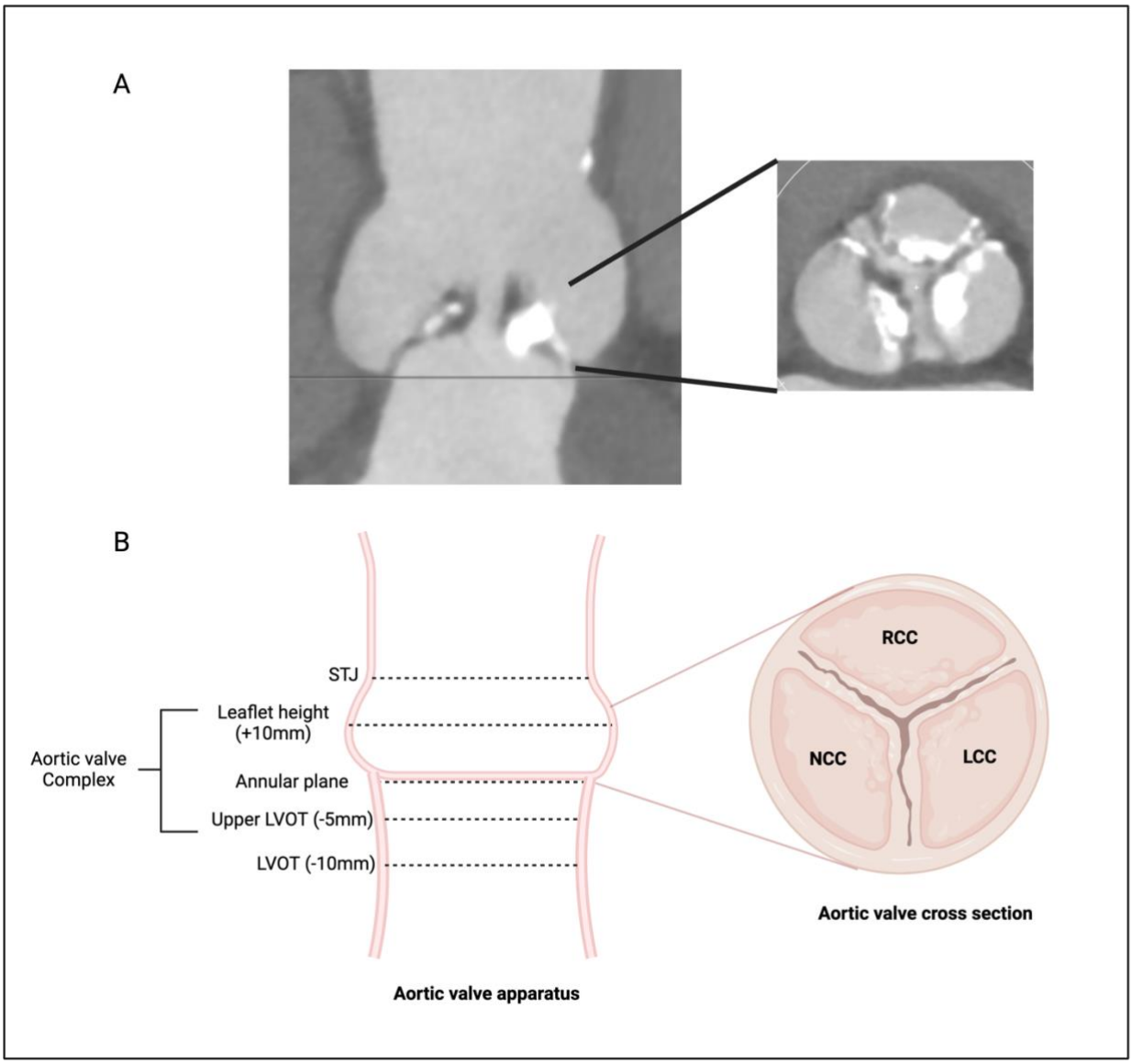


Figure 1: CT based volumetric analysis of the aortic valve apparatus. Part A demonstrates a patient's longitudinal stretched aorta vessel view (left) and the cross-section (right). Part B is a labelled schematic diagram of the same. The aortic valve complex was defined as upper LVOT (-5mm from aortic annulus) to leaflet height (+10mm from annular plane). LVOT defined as 10mm below the annular plane. RCC: right coronary cusp; NCC: non coronary cusp; LCC: left coronary cusp.

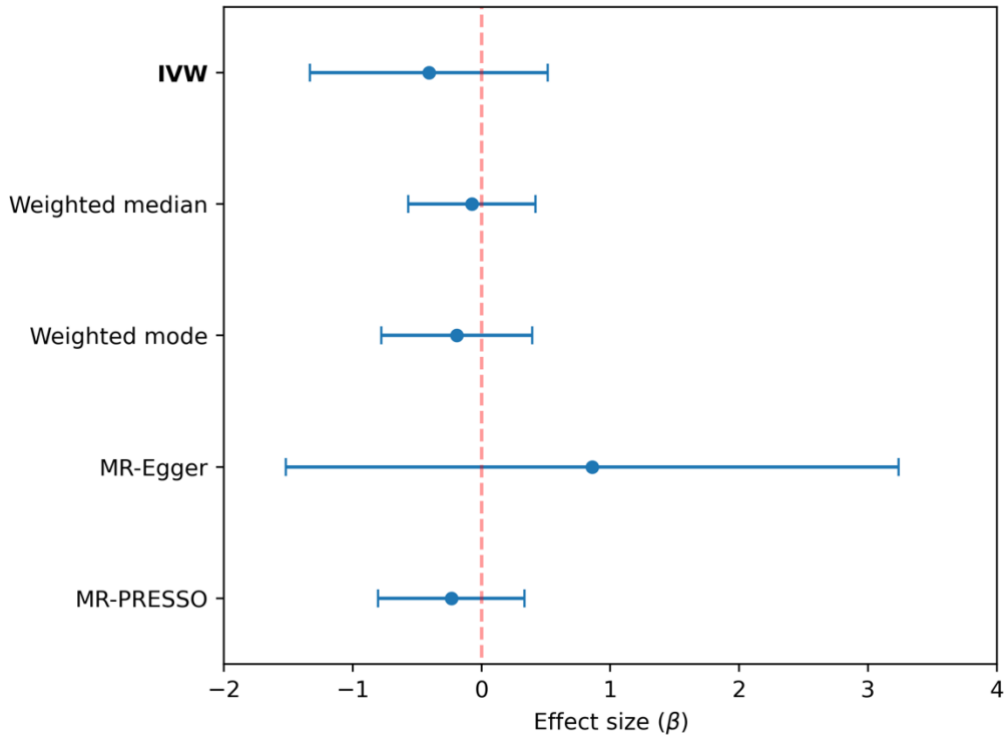


Figure 2: Mendelian randomization inverse variance weighted and sensitivity analysis estimates for the effect of genetically predicted liability of aortic stenosis on PR interval duration.

Table 1: Cohort demographics, echocardiographic, ECG and electrophysiology data
BMI: body mass index; STS: Society of Thoracic Surgeons; HR: heart rate; SD: standard deviation; AV: atrioventricular; RBBB: right bundle branch block; LBBB: left bundle branch block; LAFB: left anterior fascicular block; LPFB: left posterior fascicular block.

Demographics	**n = 196**
Age, years (mean, SD)	81.8 (6.3)
Gender (Male) (n, %)	127 (64.8)
BMI (kg/m^2) (mean, SD)	27.58 (5.3)
STS Risk Score (%) (median, IQR)	2.78 (2.99)
EuroScore II (%) (median, IQR)	2.33 (1.89)
Hypertension (n, %)	159 (81.1)
Hypercholesterolaemia (n, %)	117 (59.7)
Diabetes (n, %)	55 (28.1)
Coronary Artery Disease (n, %)	69 (35.2)
Coronary artery bypass grafting (n, %)	20 (10.2)
Peripheral Arterial Disease (n, %)	11 (5.6)
Previous Stroke (n, %)	17 (8.7)
Chronic obstructive pulmonary disease (n, %)	21 (10.7)
Chronic Kidney Disease (n, %)	55 (28.1)
Any prior atrial fibrillation / flutter (n, %)	61 (31.1)
Beta blocker (n, %)	72 (36.7)
Non-dihydropyridine calcium channel blocker (n, %)	12 (6.1)
Mean aortic valve gradient, mmHg (median, IQR)	42.0 (15.0)
Aortic valve area, cm^2 (median, IQR)	0.80 (0.29)
Cohort ECG and electrophysiology results	
HR (bpm) (mean, SD)	72.0 (13)
Presenting Rhythm (n, %)	
Sinus rhythm	113 (57.9)
Atrial fibrillation or flutter	36 (18.5)
1st degree AV block	46 (23.6)
2^{nd} or 3^{rd} degree AV block	0 (0)
PR Interval (ms) (mean, SD)	183.5 (33.1)
AH Interval (ms) (mean, SD)	109.7 (34.8)
HV Interval (ms) (mean, SD)	58.6 (10.9)
QRS Interval (ms) (mean, SD)	100.2 (26.3)
Interventricular conduction delay (n, %)	
None	132 (67.7)

RBBB	30 (15.3)
Bifascicular block + RBBB	10 (5.1)
LBBB	12 (6.1)
LAFB	17 (8.7)
LPFB	1 (0.5)
Incomplete RBBB	1 (0.5)
Incomplete LBBB	2 (1.0)

Table 2**:** Relevant demographics and echocardiographic parameters by presenting rhythm. BMI: body mass index**;** AV: aortic valve; AVA: aortic valve area; LVEF: left ventricular ejection fraction; AVC: aortic valve calcium; SD: standard deviation; IQR: interquartile range.

CT: computed tomography; AV: atrioventricular; STS: society of thoracic surgery; SD: standard deviation; CI: confidence interval

Relevant demographics, echocardiogram & CT Characteristics by presenting ECG rhythm				
	Sinus rhythm (n = 113)	1st degree AV block (n = 46)	Odds Ratio (95% CI)	*P*-value
Age (years), mean, (SD)	81.2 (6.8)	83.0 (4.9)	1.05 (0.99-1.11)	0.11
Gender Male, n (%)	68 (59.6)	31 (67.4)	0.72 (0.35-1.47)	0.36
BMI, mean (SD)	27.4 (5.5)	28.0 (5.5)	1.02 (0.96-1.08)	0.60
Echocardiographic characteristics				
Septal Thickness (cm) (mean, SD)	1.2 (0.2)	1.4 (1.6)	1.39 (0.71-2.7)	0.34
AV Mean Gradient (mmHg) (mean, SD)	48.1 (17.0)	41.1 (12.7)	0.96 (0.93-0.99)	0.01*
AVA (Continuity) (cm^2) (mean, SD)	1.5 (7.8)	0.8 (0.2)	0.96 (0.81-1.15)	0.68
LVEF (%) (mean, SD)	59.4 (8.4)	60.0 (7.3)	0.69 (0.97-1.04)	0.69
Medications influencing atrioventricular function				
Beta blocker, n (%)	36 (31.6)	14 (30.4)	0.95 (0.45-1.99)	0.89
Non-dihydropyridine calcium channel blocker, n (%)	4 (3.5)	5 (10.9)	3.35 (0.86-13.10)	0.08
CT Characteristics				
Total AVC Calcification, median (IQR)	760.5 (585.5)	717.0 (651.5)	1.0 (0.99-1.001)	0.62
Total LVOT Calcium, median (IQR)	14.0 (82.0)	0.0 (49.0)	0.99 (0.98-1.00)	0.18
AVC: NCC Calcium volume, median (IQR)	332.0 (303.0)	265.0 (280.0)	0.99 (0.99-1.00)	0.31
AVC: LCC Calcium volume, median (IQR)	168.5 (221.5)	181.0 (161.0)	1.0 (0.99-1.00)	0.73
AVC: RCC Calcium volume, median (IQR)	192.0 (253.0)	237.0 (203.0)	1.0 (0.99-1.00)	0.75

Table 3**:** Multi-variable linear regression of the primary outcome (Total AVC Calcium volume) with markers of atrioventricular conduction (PR, AH and HV intervals) adjusting for age, gender and aortic valve mean gradient.

EPS: electrophysiology study; AVC: aortic valve complex; LVOT: left ventricular outflow tract; NCC: non-coronary cusp; LCC: left coronary cusp; RCC: right coronary cusp

	Regression coefficient (β)	Standard Error	*P*-Value
Outcome: PR Interval			
Total AVC Calcium (mm^3)	0.006	0.008	0.476
Age (years)	0.505	0.462	0.277
Gender	-7.107	6.661	0.288
Aortic valve mean gradient (mmHg)	-0.286	-0.136	0.138
R^2: 0.041 F-Ratio: 1.501 (p = 0.205)			
Outcome: AH Interval			
Total AVC Calcium (mm^3)	0.006	0.008	0.410
Age (years)	1.273	0.467	0.007*
Gender	-7.071	6.700	0.293
Aortic valve mean gradient (mmHg)	-0.244	0.193	0.293
R^2: 0.080 F-Ratio: 2.981 (p=0.021)			
Outcome: HV Interval			
Total AVC Calcium (mm^3)	0.002	0.002	0.254
Age (years)	0.159	0.133	0.235
Gender	-1.644	1.956	0.402
Aortic valve mean gradient (mmHg)	-0.065	0.056	0.402
R^2: 0.033 F-Ratio: 1.471 (p=0.213)			
Outcome: AV Wenckebach up to 120 BPM*			
	Odds Ratio (95% CI)	P Value	
Total AVC Calcium (mm^3)	1.00 (1.00-1.01)	0.400	
Age (years)	1.07 (1.01-1.15)	0.032	
Gender	0.47 (0.19-1.19)	0.113	

Aortic valve mean gradient (mmHg)	0.98 (0.95-1.01)	0.147
**Pacing conducted at baseline heart rate or 70 beats per minute (whichever faster) and continued in 20 beat salvos in 10 beats per minute increments until 120 beats per minute*		

*****Coefficients are unstandardized

Data availability statement:
The data used in the Mendelian randomisation analyses are publicly available. Summary statistics for aortic stenosis are available from: https://doi.org/10.5281/zenodo.7505361; PR interval from: https://cvd.hugeamp.org; heart failure from: https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018806/; and AV block from https://r9.finngen.fi

Disclosure statement: M. N. reports travel reimbursements and honoraria from AstraZeneca (not relevant to this manuscript). All other authors declare no competing interests.

Funding statement: This study was self-funded by the Royal North Shore Cardiology Department (Sydney, Australia). The mobile electrophysiology system (EP Perfect) was loaned by BIOTRONIK (Berlin, Germany). This is an investigator initiated and led clinical trial. K. Rao is supported by National Health and Medical Research Council (NHMRC) and Heart Research Australia (HROz) PhD Scholarships. M. N. is supported by a research fellowship from the British Heart Foundation (grant number FS/IPBSRF/22/27060). K. Rahimi reports grants outside the submitted work from the British Heart Foundation, Horizon Europe AI4HF consortium (R79992/CN001), Novo Nordisk Oxford Big Data Partnership University of Oxford, the National Institute for Health Research Oxford Biomedical Centre, Oxford Martin School and UKRI's Global Challenge Research Fund Grant Ref: ES/P011055/1. K. Rahimi has previously received consulting fees from Medtronic CRDN, and honoraria or fees from BMJ Heart, PLoS Medicine, AstraZeneca MEA Region, Medscape and WebMD Medscape UK. All other authors declare no relevant funding.

Author Statement: KRao (conceptualisation, methods, writing). JC (conceptualisation, methods, writing). DH (methods, data curation); MN (data curation), KRahimi (editing); AB (editing); NS (data curation); PNL (data curation); UA (editing); PH (editing); RB (editing, supervision).

Acknowledgements: Nil.

SECTION IV: BROADER PROCEDURAL AND MANAGEMENT CONSIDERATIONS FOLLOWING TAVI

Section Introduction: Broader procedural and management issues after TAVI

In addition to investigating and refining the prediction of conduction disease following TAVI, there are several broader procedural and management considerations which were explored during my PhD candidature and will be discussed in this section of the thesis. Recently, TAVI indications have expanded, with randomised control trials such as PARTNER III(36) and Evolut LOW-RISK(76) demonstrating non-inferiority in low-surgical risk groups. The NOTION(23) study has shown non-inferiority up to 10 years for self-expandable prostheses, however we wait for long-term durability outcomes in low-risk patients and with other valve types. Australia's approval of low-risk TAVI in 2022 has resulted in increased treatment of younger and healthier patients, who are more likely to outlive their first valve, and require pre-procedural consideration of their future treatment options.

Chapter 10 is a published *Expert Review* which discusses lifetime planning considerations, emphasizing pre-procedural computed tomography (CT) imaging to help implanters future-proof patients likely to outlive their first valve. Initial priorities include optimizing the index procedure for maximal hemodynamic function and durability, minimizing new pacemaker implants, reducing paravalvular regurgitation, and preventing complications such as coronary obstruction and annular rupture. For patients requiring a second valve procedure, a significant proportion will face TAVI-in-TAVI challenges, necessitating careful planning to address potential risks and individualize lifetime care.

The second major implication of the widespread adoption of low-risk TAVI has been the increased demand of hospital systems. In 2021, the cost of TAVI in Australia was approximately $53,164 AUD, based on an average five-day hospital stay. Although the median length of stay has gradually decreased, bed availability in the public sector remains a

challenge. Implementing same-day or next-day discharges for *select* low-risk patients may enhance bed utilization and efficiency. Early discharge can support patient recovery, helping to prevent deconditioning, delirium, and infections. The 2019 Vancouver 3M(101) demonstrated that next-day discharge after TAVI with balloon-expandable valves was safe for 80% of selectively chosen patients, potentially reducing healthcare cost by up to 20%. Furthermore, studies during the COVID-19 pandemic highlighted the safety of same-day discharge in patients undergoing minimalist transfemoral TAVI. Chapter 11 is a recently accepted manuscript, which seeks to hypothetically implement a locally derived same-day discharge pathway to assess its feasibility in a low-risk Australian TAVI cohort and pave the way for prospective study. Building from the positive results of this retrospective feasibility assessment, our research group is now conducting a prospective assessment of the same locally derived same-day discharge pathway at our local centre.

Lastly, Chapter 12 is a published retrospective study, which focuses on valve frame infolding, a rare but serious complication which was observed during my PhD candidature. This study examines high infolding incidence in patients with large, calcified annular anatomy receiving the 34mm Medtronic Evolut Pro Plus system, which was subsequently brought to the attention of the manufacturer, and recalled due to safety concerns.

CHAPTER 10: Lifetime management considerations to optimise transcatheter aortic valve implantation: a practical guide

EuroIntervention
2024;20:e1493-e1504
published online e-edition December 2024
DOI: 10.4244/EIJ-D-24-00332

EXPERT REVIEW

Lifetime management considerations to optimise transcatheter aortic valve implantation: a practical guide

Karan Rao[1-3], MD, BMed, MPH; Alexandra Baer[2], MSN, MSHM; Vinayak N. Bapat[4], MBBS, MS, MCh; Nicolo Piazza[5], MD, PhD; Peter Hansen[1,2], MBBS, PhD; Bernard Prendergast[6,7], DM; Ravinay Bhindi[1-3]*, MBBS, PhD

**Corresponding author: Department of Cardiology, Royal North Shore Hospital, Reserve Road, St. Leonards, Sydney, NSW, 2065, Australia. E-mail: Ravinay.bhindi@sydney.edu.au*

Published in:

EuroIntervention (2024) Volume 20, Number 24. e1493-e1504

Author contribution statement:

This chapter is published work for which I was first author. I conceived the key ideas of the review and drafted the concepts in the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Lifetime management considerations to optimise transcatheter aortic valve implantation: a practical guide

Karan Rao MD BMed MPH[1, 2, 3], Alexandra Baer MSN MSHM[2], Vinayak N. Bapat MBBS MS MCh[4], Nicolo Piazza MD PhD[5], Peter Hansen MBBS PhD[1, 2], Bernard Prendergast DM[6] & Ravinay Bhindi MBBS PhD[1, 2, 3]

[1] Royal North Shore Public Hospital, Sydney, Australia

[2] North Shore Private Hospital, Sydney, Australia

[3] University of Sydney, Sydney, Australia

[4] Abbott Northwestern Hospital, Minneapolis, Minnesota, USA

[5] McGill University Health Centre, McGill University, Montreal, Quebec, Canada

[6] Department of Cardiology, St Thomas' Hospital, London, United Kingdom; Heart, Thoracic and Vascular Institute, Cleveland Clinic, London, United Kingdom

Short Title: Lifetime management of TAVI

Corresponding Author:

Professor Ravinay Bhindi

Ravinay.bhindi@sydney.edu.au

Department of Cardiology, Royal North Shore Hospital

Reserve Road, St. Leonards, 2065, Sydney, Australia

10.1 Abstract

Transcatheter aortic valve implantation (TAVI) is a safe and effective procedure for treatment of aortic stenosis. With the recently broadened indications, there is a larger cohort of patients likely to outlive their first transcatheter heart valve (THV). This review discusses relevant lifetime planning considerations, focussing on the utility of pre-procedure computed tomography (CT) imaging to help implanters future-proof their patients likely to outlive their first valve. The initial priority is to optimise the index procedure by maximising THV haemodynamic function and durability. This involves maximising the effective orifice area, minimising the risk of new pacemaker implantation, reducing paravalvular regurgitation, and preventing coronary obstruction and annular rupture. In patients requiring a second valve procedure, a significant proportion will require a TAVI-in-TAVI, and implanters should consider the key priorities for a redo procedure, including the increased risk of patient prosthesis mismatch, conduction abnormalities, promoting coronary re-accessibility, and preventing coronary obstruction and sinus sequestration. Careful planning can identify potential hurdles as well as predict the feasibility and likely outcomes of re-do TAVI, to help individualise care over the lifetime of each patient.

Abbreviations

TAVI: transcatheter heart valve; THV: transcatheter heart valve; AS: aortic stenosis; CT: computed imaging; ECG: electrocardiography; PPM: patient prosthesis mismatch; PVL: paravalvular leak; STJ: sino-tubular junction

10.2 Introduction

Transcatheter aortic valve implantation (TAVI) is a safe and effective procedure for symptomatic severe aortic stenosis (AS) that is increasingly offered to patients who are younger and at low surgical risk. Long term safety and efficacy of TAVI compared to surgical aortic valve replacement (SAVR) has been demonstrated in the PARTNER 3 (5 years), Evolut Low Risk (4 years) and NOTION (10 years) studies(21-23), whilst the recently published DEDICATE study is the first non-industry sponsored randomised controlled trial to show non-inferiority of TAVI compared to SAVR in low and intermediate risk patients up to 1 year(176).

The most recent American College of Cardiology/American Heart Association guidelines recommend TAVI for patients aged >80 years and suggest shared decision making to determine the choice between TAVI and surgical aortic valve replacement (SAVR) in those aged 65 – 80 years(24). In contrast, the European Society of Cardiology/European Association of Cardiothoracic Surgery (ESC/EACTS) guidelines suggest TAVI in patients aged 75 years or more and SAVR in younger patients at low surgical risk, with shared decision making in other patients according to clinical, anatomical and procedural factors(253). These broadened indications have resulted in a larger cohort of patients with fewer comorbidities and longer life expectancy, who are likely to outlive their first transcatheter heart valve (THV) and require a second procedure.

There is now increasing appreciation of the need for carefully planned lifetime management of AS. Whilst seemingly obvious, lifetime planning begins with optimisation of the *first* procedure to maximise THV haemodynamic function and durability. Precise pre-procedural measurements derived from computed tomography (CT) can help implanters to choose an optimal THV to maximise effective orifice area, minimise the need for pacemaker

implantation, reduce paravalvular regurgitation, and avoid coronary obstruction and annular rupture.

In patients expected to outlive their first THV, the choice of valve as well as the depth of implantation are to the feasibility of a re-do procedure. This review discusses relevant planning considerations prior to TAVI to help implanters future-proof their patients who are likely to outlive their first valve (Central Illustration). Part 1 summarises key priorities to optimise the first implant, whilst Part 2 discusses specific TAVI-in-TAVI considerations.

10.3 Part 1: Optimising the initial procedure

Patient prosthesis mismatch

Patient prosthesis mismatch (PPM) occurs when the prosthesis orifice area is too small for a given patient's body size and is evaluated by indexing the effective orifice area (iEOA), to the patient's body surface area (BSA). PPM is generally defined by an iEOA $<0.85 cm^2/m^2$ (severe PPM $\leq 0.65 cm^2/m^2$).

With improved THV design and more accurate CT-guided valve sizing, the incidence of severe PPM has steadily dropped, with a rate of 6.3% in current generation devices(254). Severe PPM is associated with all-cause and cardiac mortality related to poorer valve haemodynamics and elevated afterload with reduced regression of left ventricular mass(255). In contrast, mild or moderate PPM does not appear to increase mortality after TAVI(256). The highest risk of PPM is in patients at extremes of body size or with very small aortic annuli(257). The recently published SMART randomised control trial(258) showed superiority of self-expanding valves (SEV) compared to balloon-expandable valves (BEV) in annuli $\leq 430 mm^2$ with respect to bioprosthetic valve dysfunction, although there were no reported clinical differences at 1 year.

Hahn *et al.* (2019)(259) published THV design and size specific post-TAVI haemodynamics, generated from core laboratory-adjudicated values for both BEV and SEV. Till date, this serves as the most comprehensive reference for implanters to predict PPM after TAVI, as well as guidance on the most reproducible measurement technique. These prediction models were assessed by a large prospective Swiss registry, which found predicted iEOA corresponded to a lower severity of PPM compared to measured iEOA, however found no increased risk of death over a median follow up of 429 days(260). Other key takeaways from Hahn *et al.*'s

paper include recommendations on assessing longitudinal valve function via comparison to the patient's prior haemodynamics rather than absolute change alone.

In smaller annuli, implanters may be influenced to choose a SEV but in low surgical risk patients with greater life-expectancy, careful consideration should also be given to SAVR with root enlargement which may help facilitate future valve-in-valve procedures(261).

Paravalvular leak

The incidence of paravalvular leak (PVL) has dropped steadily over the past decade due to the use of multi-planar CT and improvements in valve engineering improving annular sealing(262). Insufficient oversizing, under-expansion, annular ellipticity as well as total or asymmetric aortic valve complex calcium has been linked with clinically significant PVL, whereas with improvements in valve skirt design, implantation depth no longer appears to be a significant predictor(54). With regards to valve choice, BEV appear to have a lower incidence of PVL compared to SEV(54).

Whilst there is consensus regarding reduced 5-year mortality with moderate or greater PVL, the long-term outcomes of mild PVL are unclear. Whilst some studies suggest increased mortality and rehospitalisation, others have shown no difference compared to patients with no PVL(263).

Minimising conduction abnormalities

Avoidance of a pacemaker is a priority in patients with greater life expectancy, since pacemaker implantation independently increases all-cause mortality and heart failure re-

hospitalisation(264), likely as a consequence of pacemaker-induced cardiac dyssynchrony and lead-related tricuspid regurgitation.

Careful review of the pre-procedure CT allows accurate annular sizing and provides information on the risks and benefits of relative over-sizing, which is associated with post-TAVI abnormalities. The membranous septum forms the non-muscular superior portion of the interventricular septum within the *inter-leaflet triangle* at the base of the non and right coronary cusps. The Bundle of His is exposed as it traverses and bifurcates along its inferior margin, and the infra-annular membranous septum length (IA-MSL) has consequently been described as a surrogate marker which may be measured on CT. Two other anatomical variants of the AV-His complex have also been described, with potential ramifications – the first (affecting 30% of individuals) was described by Kawashima and Sasaki in 2005(51) and may be protective since the His bundle is shielded, as it extends inferiorly into the muscular ventricular septum. In contrast, the second less common variation (affecting 20%) may result in a perilously *exposed* His traversing under a thin layer of sub-endocardium in the membranous septum – the so called “naked” His bundle.

The IA-MSL can be accurately and reliably measured on CT, and whilst various methods exist, a reproducible technique(49) involves placing the crosshair between the non and right coronary cusp on an axial view of the aortic root in an appropriately gated systolic-phase image to isolate the inter-leaflet triangle and visualise the membranous septum on the stretched-vessel plane (Figure 1). Absolute IA-MSL <3mm(49), and an implant depth greater than the IA-MSL(46), are published predictors of pacemaker implantation after TAVI.

Valve implant depth along with LCC calcification at the LVOT level have been described as predictors of pacemaker dependency(265). More than half of the patients requiring an acute permanent pacemaker after TAVI are not dependent at 1 year, secondary to recovery of the conduction pathway. The benefit of preventing pacemaker dependency is amplified in patients with longer life expectancy, as dependency has been associated with significantly increased mortality at extended follow up(266). In pacemaker-dependent patients, conduction system pacing, particularly through left bundle branch pacing may be superior to other techniques and reduce the risk of pacemaker induced cardiomyopathy(267). SEVs have historically resulted in comparatively higher pacemaker rates compared to BEVs, but this gap appears to be closing with the *cusp overlap* technique that facilitates an accurate and higher implantation depth(268). Novel methods using preprocedural computed simulation may further assist in predicting the risk of post-TAVI conduction abnormalities as well as PVL. Existing studies have simulated future THV force on the LVOT (maximum contact pressure) and the proportional area subjected to that force (contact pressure index) with good correlation between these indices and the likelihood of pacemaker implantation, and appropriate valve sealing(65).

By incorporating the IA-MSL, calcium distribution and valve oversizing with established electrocardiographic predictors (such as pre-existing right bundle branch block), operators can make an *informed* decision on initial valve choice and implantation depth to help reduce pacemaker rates and dependency.

Risk of coronary obstruction and feasibility of coronary access

Coronary obstruction is a rare but serious complication of TAVI that arises in 0.6% of native valve procedures(269) with a 30-day mortality of up to 50%. Obstruction occurs as a result of

displacement of the pre-existing native leaflet, or, less commonly, occlusion by the inferior THV skirt, and may be a *direct* consequence of leaflet induced coronary obstruction or *indirect,* via sealing of the sino-tubular junction (STJ) and *sequestration* of the coronary sinus. Anatomical risk factors include low-lying coronaries, a shallow STJ or coronary sinus, and bulky calcified leaflets, whilst procedural risk factors include high implantation depth and valve-in-valve implantation within a prior surgical bio-prosthesis(270). The current literature is mixed with regards to valve choice to prevent coronary obstruction(269, 271) .

Reliable prediction of coronary obstruction is nuanced and requires careful pre-procedural CT planning to understand the unique interplay between the coronary ostia, sinus, leaflets and STJ in each patient (Figure 2). Furthermore, it requires appreciation of the dimensions, design, and implantation depth of the intended THV. A recently published score validated the use of three CT-derived predictors of coronary obstruction, with > 90% specificity and sensitivity in patients with coronary cusp height greater than coronary ostial height, *and* virtual VTC distance ≤ 4mm, *or* culprit leaflet calcification >600mm^3 (272).

Supra-annular valves with higher commissural posts and greater risk of reaching the coronary ostia and STJ pose increased risk of coronary obstruction compared to annular valves(271). Whilst mis-aligned supra-annular valves (such as the Evolut and Acurate Neo2 platforms) pose the greatest danger of coronary obstruction, this risk may be partly offset via reliable commissural alignment(273). Commissural alignment may be challenging in patients with eccentric coronary ostia or using current generation Sapien or Portico platforms. However, it may be feasible with the upcoming Sapien X4, which is not yet commercially available but under current evaluation in the ongoing ALLIANCE safety and efficacy study (NCT05172960).

The "*snorkel*" (or "*chimney*") stent technique or BASILICA leaflet modification (bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction) should be considered in patients with high-risk features for coronary obstruction. The "*snorkel*" technique maintains coronary flow via a stent protruding from the coronary ostium back into the aorta, whereas BASILICA uses electrocautery to lacerate and splay the associated aortic leaflet. Preliminary head-to-head data suggest high efficacy rates of both techniques with comparable outcomes at 1 year, but long term data is not yet available(274).

Annular Rupture

Annular rupture is a rare but potentially fatal complication of TAVI that is more common with BEV(275). CT sizing and anatomical characterisation with precise annular measurement have assisted in reducing its incidence.

The aortic apparatus is a dynamic structure that fluctuates in size over the course of the cardiac cycle, and the largest measurements are therefore obtained in systole. BEV are routinely sized based upon annular area and oversized at 0-10%, whereas SEV employ a perimeter-based sizing algorithm and are over-sized at 10-25%. Whilst reducing paravalvular leak and optimising iEOA, excessive valve oversizing increases the risk of annular rupture.

Sub-annular LVOT calcification presents the greatest risk of annular rupture, especially when nodular calcification is located adjacent to the left fibrous trigone and left/right commissure(276). The greatest risk is with BEV(277), whereas SEV are rarely associated with annular rupture unless aggressive pre- or post-dilatation is undertaken. In this situation,

balloon sizes should not exceed the mean diameter of the LVOT or STJ (whichever is *smaller*) with a balloon: artery ratio of 1 for semi-compliant and <1 for non-compliant balloons(277).

Figure 3 summarises a basic framework for valve preference with commonly experienced patient and anatomical scenarios.

Leaflet thrombosis

Leaflet thrombosis is a reversible and dynamic phenomenon. Initial subclinical changes comprise of hypo-attenuated leaflet thickening (HALT), which may progress to restricted leaflet motion and bioprosthetic valve failure. A triad of hypercoagulability on the bioprosthetic surface, leaflet endothelial damage during device deployment, and stasis and turbulent flow may lead to HALT, which may occur in up to 12% of all TAVI cases(278). A 2021 meta-analysis(279) found intra-annular valves were associated with a 2-fold greater risk of subclinical leaflet thrombosis compared to supra-annular platforms. Untreated leaflet thrombosis was associated with a 2.6-fold increase in stroke, whilst a switch to anticoagulation resulted in resolution in 99% of cases. There is currently no data advocating for prophylactic anticoagulation to prevent HALT.

Predicting feasibility of TAVI-in-TAVI

In patients with extended life-expectancy, it is paramount to predict the feasibility of TAVI-in-TAVI using the index CT. As Figure 4 outlines, we propose a simple framework which incorporates the key components.

As discussed earlier, accurate CT-derived annular and LVOT sizing aids in predicting PPM. Patients with a small annulus (<400mm^2) are particularly high risk of PPM, which may be exacerbated by TAVI-in-TAVI. In patients of low-surgical risk, implanters may strongly consider a SAVR with root enlargement, to prevent the "Russian Doll" effect with future TAVI-in-TAVI. Otherwise, the results of the recently published SMART study may sway implanters towards the initial use of SEV, however an understanding of the implication on future coronary access is essential.

A future TAVI-in-TAVI will create a "neo-skirt" (also known as "tube-graft") due to pinning of the index THV leaflets. Therefore, top of the index THV leaflets denotes a *risk plane,* which helps to determine the feasibility of a second THV with respect to accessing the coronary arteries. The estimated risk plane can be derived by subtracting the implantation depth from the THV leaflet height, which will differ based on valve choice, detailed in Figure 5**.** The valve leaflets extend to the top of the balloon-expanding Sapien 3 (S3) commissure tab (top of stent frame in Sapien XT), and to the top of the commissural post of self-expandable valves (Evolut R/Pro/Pro+/FX, Acurate Neo/Neo2 and Portico Navitor). The self-expandable prostheses are generally taller, whilst the Evolut and Acurate Neo2 valves are supra-annular with leaflets that extend higher than the intra-annular S3 and Portico systems.

Ideally, implanters should aim to keep the risk plane below the coronary heights, or at least below the STJ, to optimise future coronary access. Table 1 contains the highest recommended implantation depths to optimise the risk plane relative to the STJ and coronary heights when using the Sapien and Evolut platforms. The interaction of the planned valve with the CT-derived coronary and STJ measurements is integral in evaluating overall feasibility, and has been described by Medranda *et al.* (2022)(280) using post-TAVI CT simulation, and further

detailed in Figure 6. Depending on the software used for CT analysis, implanters can utilise a virtual circle or valve to visualise the relationship with surrounding aortic root structures.

10.4 Part 2: TAVI-in-TAVI Considerations

The anticipated durability of the index THV is a key consideration when planning the lifetime treatment of AS. The Valve Academic Research Consortium 3 (VARC-3) definitions of bioprosthetic valve failure include structural and non-structural valve deterioration, as well as thrombosis and endocarditis(281).

The NOTION study compared the Medtronic CoreValve to SAVR and demonstrated a lower incidence of severe structural valve deterioration (SVD) following TAVI (1.5 vs. 10% p=0.02) at 10 year follow up(23). Separately, a British registry reported a 6% incidence of *severe* SVD 8 years after TAVI, although this figure was likely driven by higher incidence in BEVs(282). Importantly, these studies assessed earlier generation THVs and are likely to overestimate the incidence of SVD associated with modern generation THVs.

Treatment options in patients with a failed TAVI include re-do TAVI or TAVI explant with subsequent SAVR. Risks associated with the latter strategy are relatively high with a 30-day mortality of 11.9% in the EXPLANT-TAVR registry (2009-2020)(283), even though the enrolled cohort were relatively complex (median STS score 5.0%, urgent procedures 54%, concomitant unrelated procedure [e.g. bypass grafting or mitral valve replacement] 55%). Nevertheless, 30-day mortality was significantly higher compared with TAVI-in-TAVI in the EXPLANTTOREDO-TAVR registry(284) (13.6% vs. 3.4% p<0.001) although landmark analysis *beyond* 30 days showed no difference at extended follow up.

A separate consideration is that the surgical risk of TAVI explant may be magnified when SEVs are extracted due to neo-endothelialisation of the taller frame within the ascending aorta(283). Despite growing experience and improved operative technique, the risks associated with TAVI explant and SAVR should be carefully balanced against the feasibility of successful TAVI-in-TAVI.

Despite its relative safety, re-do TAVI is not always the optimal treatment strategy. For example, re-do TAVI is not recommended in patients with valve failure secondary to active endocarditis, although one large study has confirmed the feasibility of TAVI as a salvage procedure in *healed* aortic valve endocarditis(285). Similarly, implantation of a second *annular* valve in patients with severe patient-prosthesis mismatch will further reduce iEOA and is therefore relatively contraindicated. Finally, patients who need concurrent cardiac surgery or are likely to require a third THV on account of their young age may be better served by TAVI explant and SAVR.

TAVI-in-TAVI: Patient-prosthesis mismatch

The risk of PPM is increased following any valve-in-valve procedure due to the *"Russian doll"* effect of multiple bioprosthetic valves. This risk is magnified in patients with a large body surface area (particularly those with a small annulus), since an initially sub-optimal iEOA will be exacerbated after implantation of a second THV. Use of an appropriately sized supra-annular THV as the second valve will provide the maximum iEOA in this situation but may risk future coronary compromise.

TAVI-in-TAVI: Managing the risk plane for coronary re-access

Failure to acknowledge the *risk plane* can lead to two possible adverse outcomes. The most dangerous is if the neo-skirt seals or *sequesters* the sinus, completely occluding coronary flow. Whilst rare, this can be fatal. The other scenario, is indirect coronary obstruction, whereby extension of the neo-skirt above the STJ or coronary ostia creates a high risk of compromised coronary flow and future difficulty in accessing the coronary ostia(286).

The optimal scenario to prevent these outcomes is to ensure the risk plane lies *below* the mid-point of the lowest coronary ostium. In cases where the risk plane lies *above* the coronary height but *below* the STJ, a VTC distance >4mm is recommended. If the risk plane extends above the STJ, then a VTC >4mm AND a valve-to-STJ distance > 2mm are required. If these criteria are not met, there is a high risk of future coronary inaccessibility(286).

To manage the risk plane and facilitate second valve choice, Grubb *et a*l(286) utilised post-TAVI CT analysis to demonstrate that the highest likelihood of preserving coronary access following re-do TAVI within an initial Evolut valve was achieved by implanting a S3 in a low position (Evolut Node 4), where only 20% cases were deemed at high risk of coronary compromise. In those with an index S3, Fukui *et al.*(287) demonstrated that second valve choice had little influence on coronary access or flow, although use of two S3 valves resulted in a substantially higher risk of at least moderate patient-prosthesis mismatch (21% vs. 1%).

Ochiai *et al.*(288) compared *high* (1-3mm) and *low* (3-5mm) depth implantation in both SEV and BEVs using post-procedural CT and confirmed that a high implant increased the risk of sinus sequestration and difficult coronary access, but lowered rates of LBBB, pacemaker implantation and paravalvular leak. These conflicting priorities associated with implantation depth therefore require a considered and individualised approach for each patient. For

example, in certain high-risk anatomies, a slightly *deeper* implant may mitigate the catastrophic outcome of sinus sequestration or coronary obstruction whilst increasing the risk of conduction abnormalities. However, it must be conceded that measurement of implantation depth is often imprecise, relying on fluoroscopic estimation that is usually performed in a two-cusp view from the nadir of the NCC to the inferior valve frame.

Although commissural alignment can help to prevent coronary obstruction during the index TAVI, reliable alignment of the second implant to the initial THV is not yet possible. In one *ex-vivo* model, strut misalignment reduced the dimensions of the accessible cell by up to 22%, thereby increasing the difficulty of future coronary catheterisation(289). Whilst Acurate Neo implantation in an S3 resulted in the *largest* accessible cell sizes, a misaligned Evolut-in-Evolut was associated with the *smallest* accessible cell sizes. The authors also highlighted the differences in neo-skirt height with various valve combinations, a duo of taller frame THVs predictably producing the highest risk plane.

TAVI-in-TAVI: Other considerations

A separate implication of a deeper second THV implant is *leaflet overhang*, with one *ex vivo* study demonstrating up to 94% leaflet overhang in S3 THVs implanted low (Node 4 – see Figure 5) within Evolut valves(290). Whilst leaflet overhang was not shown to impair redo THV function *ex vivo*, long-term outcomes and valve durability data are not yet available.

Implanters should also consider the variable *re-expansion* of the index THV following second valve implant, which may cause an inadvertent increase in the diameter of the neo-skirt. By widening and drawing the index THV closer to the coronary ostia and STJ, re-expansion may exponentially increase the risk of sinus sequestration and coronary obstruction. This

phenomenon seems to be most prominent when the S3 is implanted within the Evolut THV, resulting in an increase of up to 2.5mm in the waist diameter of the initial Evolut in bench studies(290).

As an additional tool for implanters, the Redo TAV application was released in April 2024, and is available for free download on all smartphone devices. It serves as an educational step-by-step walk-through for planning and executing TAVI-in-TAVI procedures (Bapat *et al.* Redo TAV, April 2024).

TAVI-in-TAVI Leaflet Modification

Leaflet modification has been proposed as a bailout strategy in patients with aortic valve anatomy at high risk of coronary obstruction requiring a TAVI-in-TAVI procedure. Whilst the BASILICA technique has relied on standard "off-the-shelf" equipment, specific leaflet splitting devices may streamline the procedure, and preliminary results from a study of 60 patients validating the safety and effectiveness of the ShortCut (Pi-Cardia, Rehovot, Israel) device has demonstrated no mortality at 30 days, with successful leaflet splitting in all patients(291).

The success of TAVI-in-TAVI BASILICA is strongly dependent on the index THV's commissural alignment and depth of implantation. Bench testing using current generation platforms, such as the S3 and Evolut, suggest *less reliable* leaflet splaying after laceration(292). Furthermore, there is a risk that the index THV leaflets could be pinned or "jailed" against their frame by the second, inner THV. Unfortunately, if the THVs are initially mis-aligned then the original commissural posts may continue to obstruct the coronary ostia, even after successful leaflet laceration. Cautionary use of TAVI-in-TAVI BASILICA is

therefore recommended, and the procedure should only be considered in highly selected patients who are unsuitable for alternative treatment.

10.5 Conclusions

The *Heart Team* faces several competing priorities when planning TAVI procedures that must account for individual patient anatomy and lifetime management. Whilst use of SEV may promote greater iEOA, improved haemodynamics and reduced risk of annular rupture, it may also increase the incidence of pacemaker implantation and paravalvular leak. Furthermore, initial use of a taller framed supra-annular valve in patients likely to require TAVI-in-TAVI, may create a higher risk plane that increases the subsequent risk of sinus sequestration or coronary obstruction. Conversely, whilst BEV have shorter frames, they may increase the risk of annular rupture and patient-prosthesis mismatch, the latter being compounded by a subsequent TAVI-in-TAVI procedure.

As TAVI is used increasingly in younger low surgical risk patients, there is greater onus on implanters to carefully review the index CT with the goals of optimal initial valve haemodynamics, reduced risk of conduction abnormalities, prevention of coronary obstruction, and facilitated acute and long-term coronary access. CT can identify potential hurdles, predict the feasibility and likely outcomes of re-do TAVI, and help implanters to individualise care over the lifetime of each patient.

Acknowledgements

Nil.

Sources of funding

Nil.

Disclosures

B.P. has received institutional educational and research grants from Edwards Lifesciences, and has received speaker/consultancy fees from Abbott, Edwards Lifesciences and Medtronic. V.B. has received institutional, educational and research grants, and is a consultant to Edwards Lifesciences, Medtronic, and Boston Scientific. N.P is a consultant and proctor for Medtronic.

10.6 Figures and Tables

Patient anatomy	Highest recommended implantation depth of index TAVI with SAPIEN[a] and Evolut[b] platforms			
Valve size and model	23 mm	26 mm	29 mm	26-34 mm
	S3/Ultra	S3/Ultra	S3/Ultra	Evolut R/PRO/PRO+
STJ height, mm				
10	9	>10	>10	>10
12.5	6.5	8.5	>10	>10
15	4	6	8.5	>10
17.5	1.5	3.5	6	9.5
20	0	1	3.5	7
22.5	0	0	1	4.5
25	0	0	0	2
27.5	0	0	0	0
≥30	0	0	0	0
Lowest coronary ostia height, mm				
≤7.5	>10	>10	>10	>10
9	10	>10	>10	>10
10.5	8.5	>10	>10	>10
12	7	9	>10	>10
13.5	5.5	7.5	10	>10
15	4	6	8.5	>10
16.5	2.5	4.5	7	>10
18	1	3	5.5	9
19.5	0	1.5	4	7.5

Table 1: Recommended highest implantation depths to ensure that the index valve risk plane remains below the STJ and coronary height.
The risk plane is equal to the depth of implantation subtracted from the commissural height.
Green squares indicate a relatively safe implantation depth in relation to conduction disease (<4mm).
Orange squares indicate the need for caution due to a moderately increased risk of conduction abnormalities (implant depth 4-8mm).
Red squares indicate a high risk of conduction abnormalities and/or an unfeasible implant depth (>8mm).
For orange and red squares, a VT-STJ (valve to STJ) >2mm and VT-C (valve to coronary) distance >4mm are required to confirm the feasibility of TAVI-in-TAVI.

Figures with captions

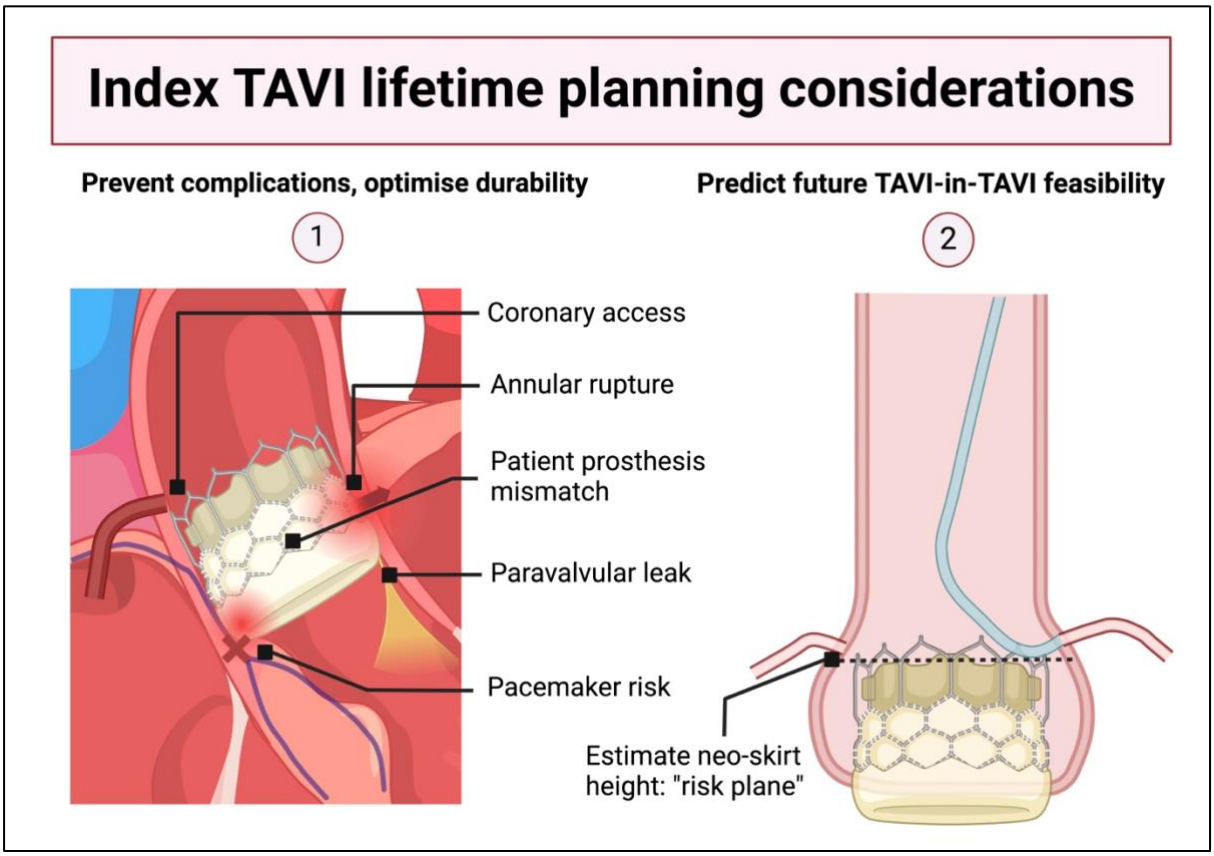


Figure: Central illustration. Index TAVI lifetime planning considerations.

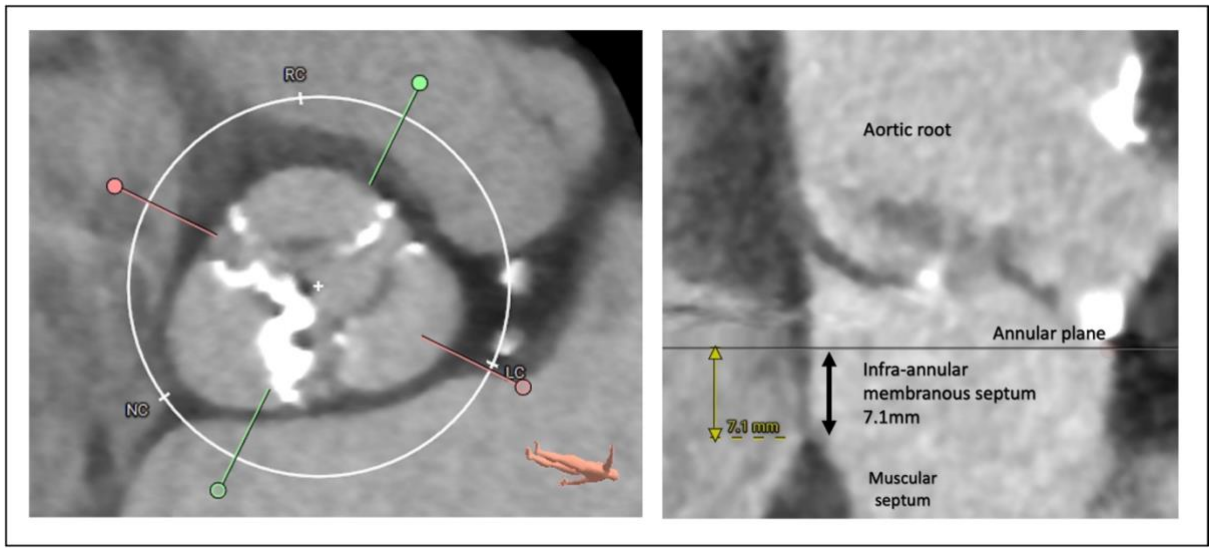


Figure 1: Identification and measurement of the infra-annular membranous septum.
Left: axial view of the aortic root showing three leaflets with a crosshair between the non-coronary cusp and right coronary cusp.
Right: corresponding “stretched-vessel” view demonstrating the inter-leaflet triangle and infra-annular membranous septum.

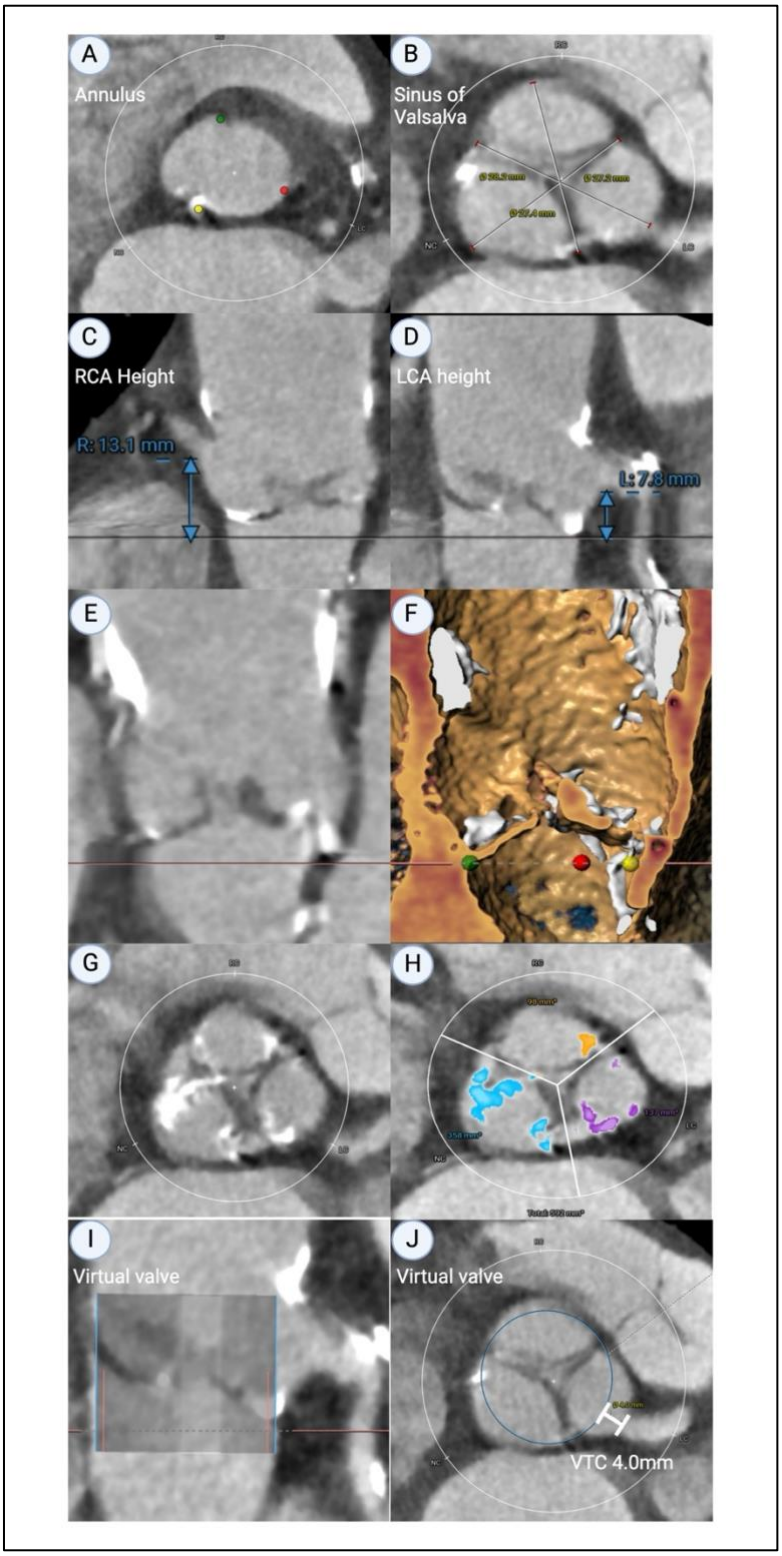


Figure 2: Relevant CT based measurements (performed on 3Mensio; Pie Medical Imaging, Maastricht, Netherlands) to aid implanters to determine the risk of coronary obstruction. A: annular dimensions for valvular sizing; B: sinus of Valsalva measurement; C: right coronary ostial height; D: left coronary ostial height; E: stretched vessel view of aortic root and calcium; F: reconstruction of corresponding stretched vessel view to visualise calcium; G & H: leaflet distribution of calcium; I: stretched vessel view of virtual valve; J: axial view of aortic root demonstrating virtual valve ring and VTC (valve to coronary) distance.

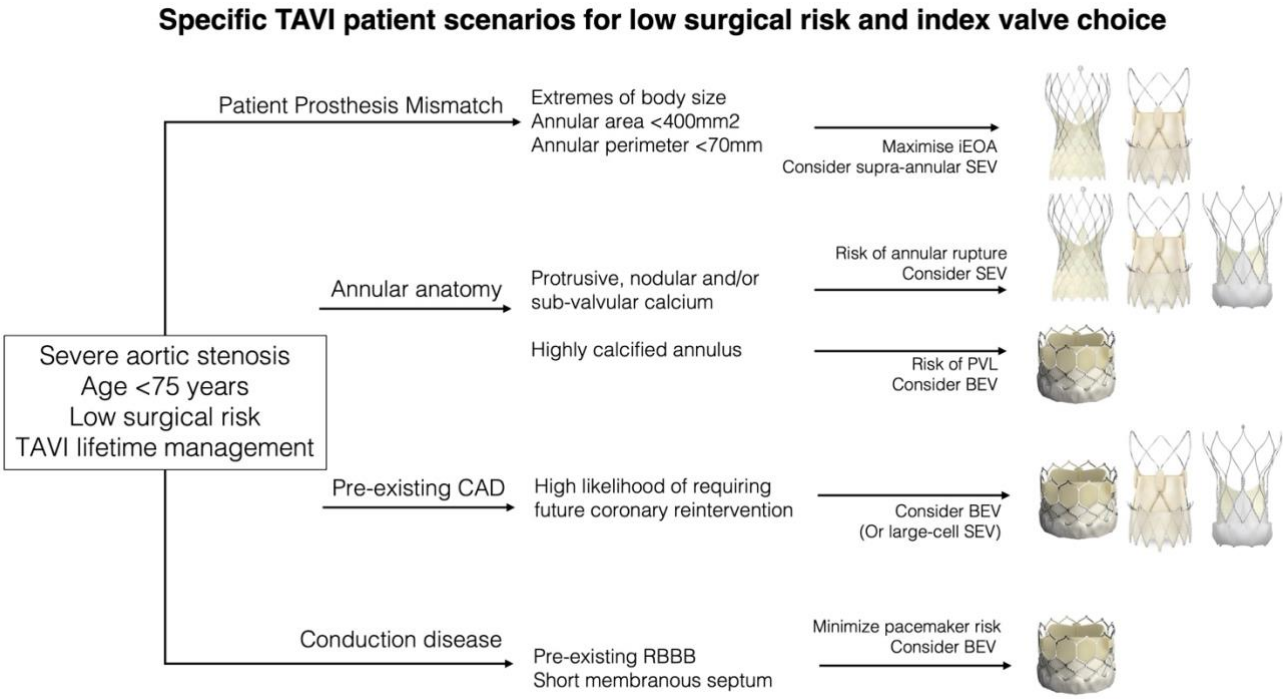


Figure 3: Commonly experienced TAVI clinical and anatomical scenarios, with preferred valve option. iEOA: indexed effective orifice area; SEV: self-expanding valve; BEV: balloon-expandable valve; PVL: paravalvular leak; CAD: coronary artery disease; RBBB: right bundle branch block.

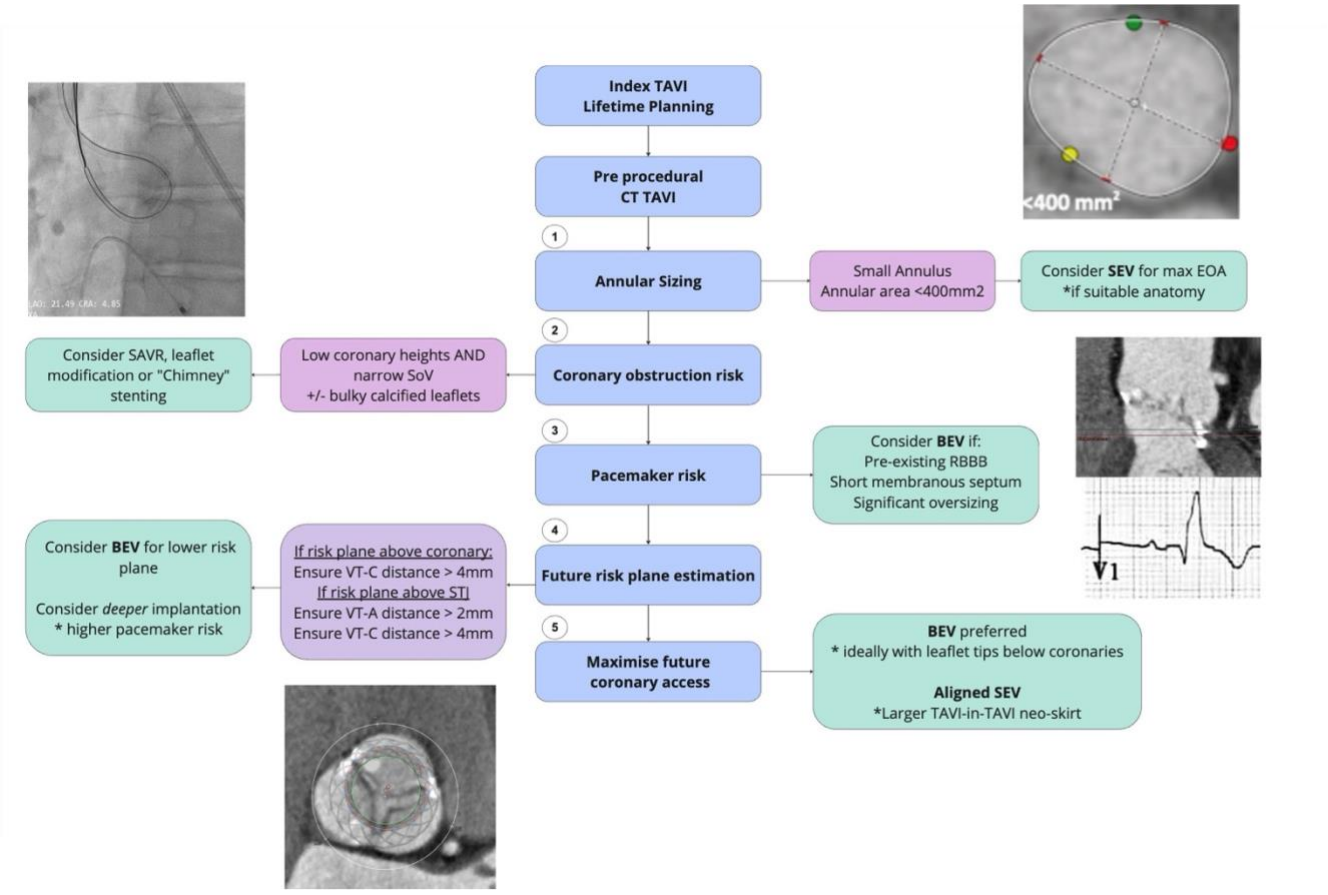


Figure 4: Stepwise approach to address factors that direct procedural planning in lifetime planning for patients undergoing TAVI. VT-A: valve to aorta distance (mm); VT-C: valve to coronary distance (mm).

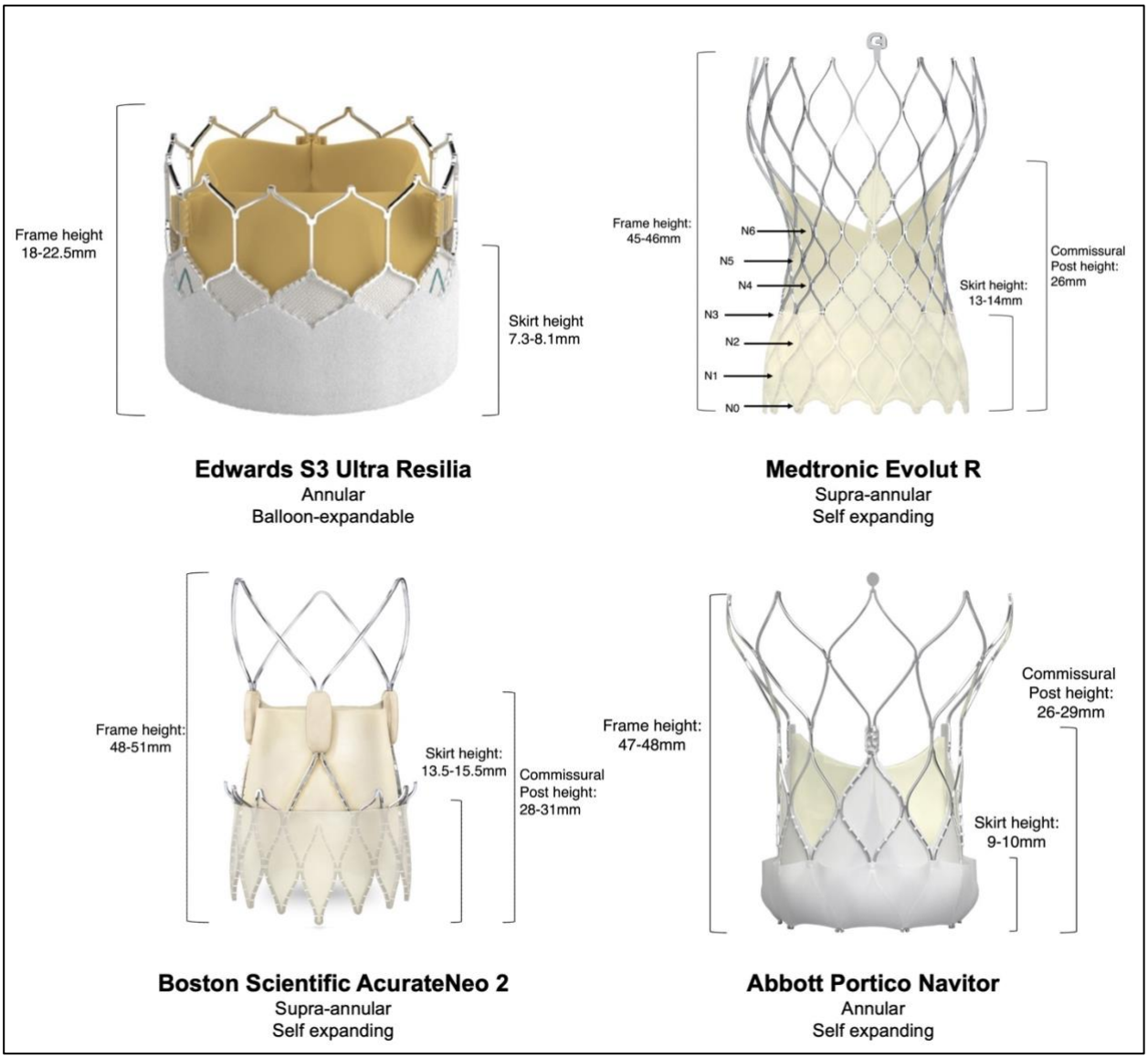


Figure 5: Modern transcatheter heart valve systems with relevant dimensions.
Edwards S3 Ultra Resilia: Medtronic Evolut R; Boston Scientific Acurate Neo2; Abbott Portico Navitor
N0-N6 refers to nodes 0-6 on the Medtronic Evolut valve, which has been used as a reference point for implant depth and second valve implant height.

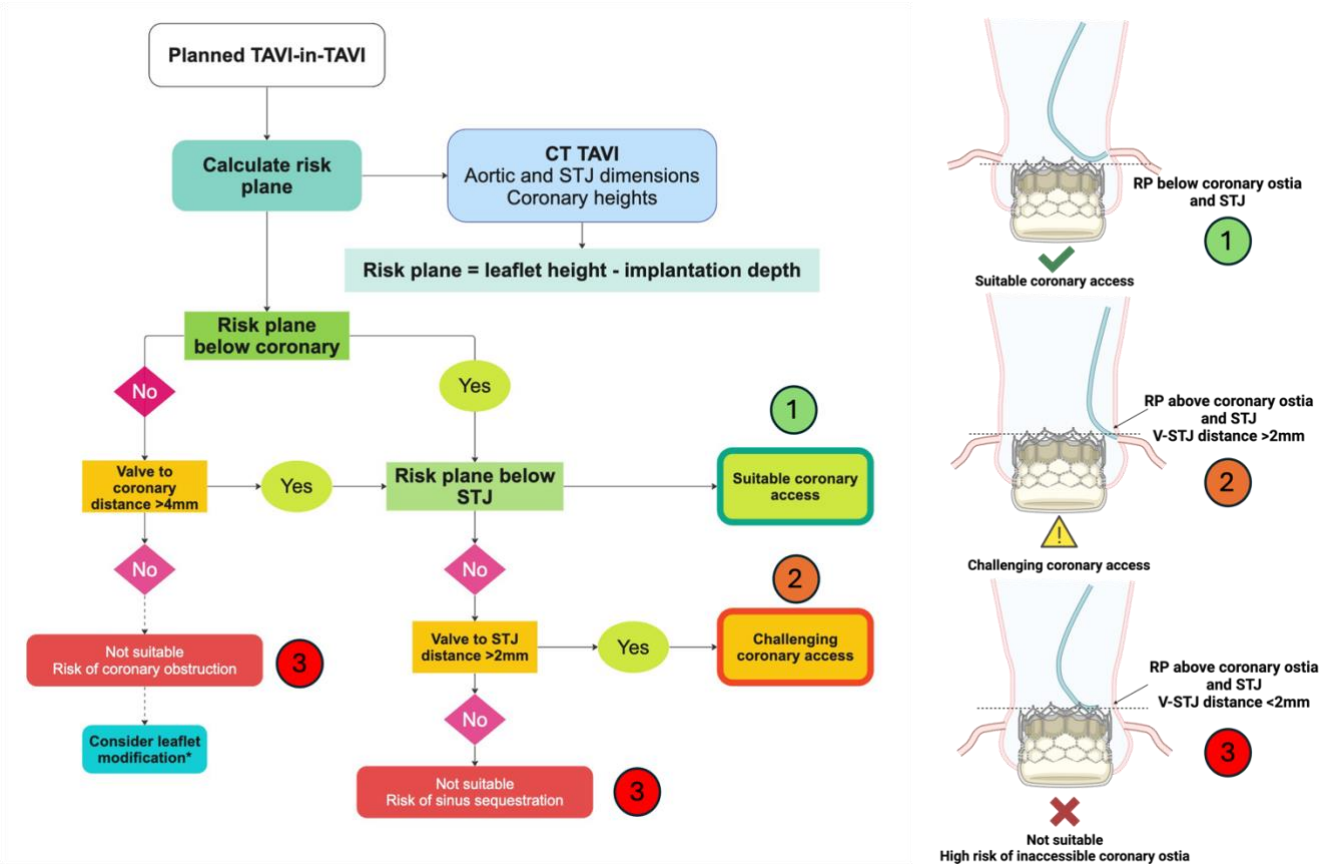


Figure 6: Determining feasibility of coronary access for TAVI-in-TAVI involves calculation of the risk plane based off aortic, STJ (sinotubular junction) and coronary dimensions on CT, followed by estimation of the implantation depth. RP: risk plane; V-STJ: valve to STJ distance.

CHAPTER 11: The feasibility of same-day discharge after transcatheter aortic valve implantation using a locally created framework in the CONDUCT-TAVI cohort

Heart and Vessels
https://doi.org/10.1007/s00380-025-02598-4

ORIGINAL ARTICLE

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Feasibility of same-day discharge after transcatheter aortic valve replacement: the North Shore Day Stay pathway

Karan Rao[1,2,3] · Princess Neila Litkouhi[1,2] · Alexandra Baer[3] · Peter Hansen[1,2,3] · Ravinay Bhindi[1,2,3]

Received: 23 June 2025 / Accepted: 3 September 2025

Published in:

Heart and Vessels. Published online ahead of print. 22nd September 2025. DOI:

10.1007/s00380-025-02598-4

Author contribution statement:

This chapter includes published work for which I was co-first author. I conceived and designed the study, collected and analysed the data (along with my co-first author Dr. Neila Litkouhi), interpreted the findings, and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Feasibility of same day discharge after transcatheter aortic valve implantation: Retrospective evaluation of the North-Shore Day Stay TAVI Clinical Pathway

*Karan Rao BMed MD MPH[1,2,3], *Princess Neila Litkouhi BMed MD[1,2], Alexandra Baer MSN MSHM[3], Peter Hansen MBBS PhD[1,2,3], Ravinay Bhindi MBBS PhD[1,2,3]

1. Cardiology department, Royal North Shore Hospital, Sydney, Australia
2. University of Sydney, Sydney, Australia
3. Cardiology department, North Shore Private Hospital, Sydney, Australia

*KR and PNL are joint first authors

Corresponding author:
Professor Ravinay Bhindi
Royal North Shore Hospital, Reserve Road, St. Leonards, 2065.
Email: ravinay.bhindi@sydney.edu.au

***Short Title**: Clinical Pathway for same-day discharge after TAVI*

11.1 Abstract

Introduction: Transcatheter aortic valve implantation (TAVI) is an effective treatment for patients with severe symptomatic aortic stenosis, however growing indications have increased the burden on the hospital system. Same-day discharge (SDD) is a proposed strategy for improved bed utilisation and hospital decongestion.

Methods: A retrospective analysis of 182 patients enrolled in a concurrently running prospective study (CONDUCT-TAVI) was performed. The locally derived North Shore Day Stay (NSDST) TAVI clinical pathway was hypothetically applied to compare those deemed suitable for SDD against those unsuitable (standard discharge cohort) with respect to clinical outcomes at 1 month.

Results: Of the 182 patients, 20 (11.0%) were deemed hypothetically suitable for SDD, whilst 162 (89.0%) were deemed hypothetically unsuitable. There were more females in the SDD cohort (55.0 vs. 21.5% p=0.04), but otherwise both groups had similar demographics and procedural characteristics. There were no differences between in-hospital, as well as discharge to 30-day outcomes. There were 3 (15.0%) readmissions in the SDD cohort of which 1 was cardiovascular (complete atrioventricular block - Day 20). There were 24 (14.8%) readmissions in the standard discharge cohort, of which 13 (8.0%) were cardiovascular. There was no stroke, bleeding or vascular site complication up to 30 days in the SDD group. The median time to discharge in the standard discharge cohort was 3 (±2) days.

Conclusions: The NSDST clinical pathway is a promising tool to stratify low-risk patients suitable for SDD after minimalist transfemoral TAVI, irrespective of valve choice. Following prospective validation, its application may substantially reduce hospital congestion.

11.2 Introduction

Transcatheter aortic valve implantation (TAVI) is an effective treatment for patients with symptomatic severe aortic stenosis. With approval in low-surgical risk, there are now more patients suitable for TAVI, placing a greater burden on an already stretched Australian hospital system. Consequently, there is a need to further streamline TAVI and improve cost-efficiency without compromising patient safety. In 2021, the cost of TAVI in Australia was estimated at $53164 (AUD), based on an average length of stay of 5 days(293). Whilst median length of stay has steadily fallen since 2021, bed availability particularly in the public sector remains challenging. A proposed strategy for improved bed utilisation is via same day or next day discharge in highly selective low risk TAVI patients. Early discharge also stands to benefit patients, as prompt mobilisation may minimise deconditioning, whilst an earlier return home could prevent delirium and nosocomial infection.

In 2019, The Vancouver 3M study(101) demonstrated that next-day discharge (NDD) after TAVI with balloon-expandable valves could safely occur in 80% of a highly selective cohort as well as reduce TAVI costs by up to 20%. They went on to also demonstrate safety of same-day discharge (SDD) in 5.9% elective transfemoral patients(294), whilst a separate North American study highlighted the retrospective safety of SDD when compared to next day discharge in transfemoral TAVI patients during the COVID-19 pandemic(121). Both studies however, predominantly used balloon-expandable valves, and there is a paucity of data assessing safety with self-expanding platforms, driven primarily by the associated increased risk of post TAVI conduction abnormalities.

This present study aims to apply a locally derived SDD pathway to demonstrate feasibility of SDD in a low-risk Australian TAVI cohort, irrespective of valve type.

11.3 Methods

Study Design & Population

Retrospective analysis was performed on 182 patients, originally enrolled into an actively running prospective study, CONDUCT-TAVI (ACTRN1261001700820). CONDUCT-TAVI recruited consecutive patients undergoing TAVI at two high-volume centres in Sydney, Australia, between October 2021 and December 2023. Patients were excluded if they had a prior permanent pacemaker (PPM) or aortic valve surgery. Furthermore, if a PPM was not required post-procedure, all patients received an implantable loop recorder prior to discharge. Further detailed information on the CONDUCT-TAVI protocol is publicly available(180). The protocol has been approved by the Northern Sydney Local Health District Ethics Committee.

The CONDUCT-TAVI cohort was chosen for this study due to the availability of extended rhythm monitoring, which was deemed necessary due to the inclusion of patients receiving self-expanding valves. Self-expanding valves have historically been a strong independent predictor of high-grade atrioventricular block (AVB) after TAVI(295) and are not well represented in current SDD studies.

TAVI Procedure

All patients underwent "*minimalist*" TAVI, which was performed under conscious sedation via the transfemoral route. Secondary access was either transradial or transfemoral, and single transfemoral transvenous access was obtained for a multipolar electrophysiology catheter for immediate pre and post TAVI targeted electrophysiology study, as mandated by the CONDUCT-TAVI research protocol. Rapid ventricular pacing was performed over the left ventricular wire in all cases. Cerebral protection devices were not used.

Pre-dilatation, valve type and size, as well as post-dilatation was at the implanters' discretion. All patients were discharged to a high-dependency unit with continuous cardiac monitoring for a minimum of 24 hours. All patients had an immediate post-procedure, 4 hour and 24-hour ECG, and underwent standard pre and post procedure echocardiography (Day 0 and Day 1).

North Shore Day Stay Clinical Pathway

The North Shore Day Stay TAVI clinical pathway (NSDST) was adapted from previously published protocols (101, 121, 296). It was retrospectively applied to all patients enrolled in CONDUCT-TAVI to assess hypothetical suitability of SDD. The protocol included preprocedural, procedural and postprocedural criteria, as illustrated in Figure 1.

Preprocedural inclusion criteria included non-urgent, elective TAVI, age ≥ 18 years, mobilising and living independently, adequate social supports to facilitate recovery at home and no significant medical comorbidities that necessitated additional in-hospital monitoring such as end stage renal disease or advanced dementia. Other exclusion criteria were all conduction-related and derived from the baseline ECG. These included a pre-existing right bundle branch block (RBBB) or atrioventricular block (AVB) (first, second or third degree). Whilst the NSDST provides an exception for patients with a prior PPM from conduction-related exclusion criteria, this was not applicable in our chosen retrospective cohort.

The procedural requirements were the use of conscious sedation (no general anaesthesia), and the absence of any high-grade AVB during valve deployment. Furthermore, patients were required to have no recorded intraprocedural complications as per the Valve Academic

Research Constorium-3 (VARC-3) criteria(297), and temporary pacing wires were required to be removed prior to the end of the case.

Postprocedural requirements were assessed at 4-6 hours post procedure and included: (1) no evidence of delirium, (2) no evidence of vascular access site complications such as haematoma or pseudoaneurysm, (3) no abnormal transthoracic echocardiogram features (LVEF > 30%, none or mild paravalvular leak, no new pericardial effusion and functioning implanted valve), (4) no new conduction abnormalities (new AVB including first degree block, or any new bundle branch block) unless patient had a permanent pacemaker, (5) ability to mobilise 20 metres (assessed using the patient's regular mobility aids) and (6) structural heart team review, together with patient and their family, to provide a final approval for SDD.

Given the retrospective nature of the present study, evidence of delirium and vascular access site complications were determined by clinical assessment which was established from medical documentation. Other studies investigating SDD in TAVI patients have used clinical examination to assess for delirium and vascular access site complications(121, 294). Similarly, mobility criteria were also assessed using medical, nursing, or allied health clinical documentation. Patients that were documented to have independently mobilised, for example, to the bathroom outside the room, were considered to have satisfied mobility criteria. Patients that remained on bedrest, required use of a bedpan, or had no explicit mention of their mobility, were considered not to have satisfied mobility criteria.

Only patients that satisfied all preprocedural, procedural and post-procedural criteria in the NSDST clinical pathway were considered suitable for SDD (SDD cohort). Patients who did

not satisfy one or more of the protocol criteria were considered not suitable for SDD (standard discharge cohort).

Outcome Measures

Detailed patient demographics were obtained and compared between SDD and standard discharge groups. This included age, sex, body mass index and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, along with medical comorbidities, prior cardiac procedures, and echocardiographic data. Baseline electrocardiography was also recorded.

Outcomes measured were in-hospital and 30-day post-discharge events, which were defined as per the VARC-3 criteria(297). The 30-day post-discharge events were defined as occurring following discharge and up to 30 days after their procedure, and included death, hospital re-admission (any cause, cardiovascular and non-cardiovascular), timing of readmission, and detailed post-discharge events including new permanent pacemaker implantation (PPMI), stroke or bleeding. Patients in the SDD cohort were compared to the standard discharge cohort at the median day of discharge for the standard discharge group, as a method to capture any potential complications in the SDD cohort that could have developed between Day 0 and standard discharge. This aimed to assess the yield of longer in-hospital monitoring for patients identified by the NSDST pathway as suitable for SDD.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Version 29.0. Categorical variables were assessed via Fisher's exact test, or a Chi-Square test. Continuous variables were reported as a mean if normally distributed and compared using a T-test, or via a median if not normally

distributed, and assessed via a Mann Whitney U statistical test. A two-tailed *p* value of <0.05 was considered statistically significant.

11.4 Results

Cohort demographics and procedural characteristics

A total of 182 patients enrolled in CONDUCT-TAVI were screened for SDD suitability. As per the original CONDUCT-TAVI criteria(180), patients received an implantable loop recorder at the conclusion of their procedure, or a permanent pacemaker in cases of high-degree AVB. The mean age of the cohort was 82.0 (±6.4) years, whilst 120 (65.9%) were male. Median STS Score was 2.6 (±1.4) corresponding to low-surgical risk. 56 (30.8%) patients had a history of prior atrial fibrillation, whilst on pre-TAVI ECG, 47 (26.0%) had first degree AVB, 31 (17.0%) had RBBB, and 12 (6.6%) had LBBB. All TAVI cases were electively performed under conscious sedation, via the transfemoral route. Self-expanding valves were most commonly used (65.4%), whilst balloon-expandable were used in 34.6%.

Predictors and safety of SDD

After application of the NSDST clinical pathway, a total of 20 (11.0%) patients were deemed suitable for SDD, whilst 162 (89.0%) were excluded and remained on the standard discharge pathway. Exclusions for SDD occurred mostly pre-procedurally (49.4%), then post-procedurally (43.8%) followed by intra-procedurally (6.8%). The most common cause for exclusion was related to conduction delay (80.9%) (Figure 2).

A greater proportion of female patients were suitable for SDD (55% vs. 21.5% p=0.04). Otherwise, there were no demographic differences between the groups (Table 1). Similarly,

procedural characteristics, including valve type, membranous septum length, annular measurements, implantation depth, and valve oversizing (%) were similar across both groups (Table 2).

There were no significant differences between SDD and standard discharge groups when comparing in-hospital outcomes, as well as discharge to 30-day outcomes (Table 3). There were 3 (15.0%) hospital readmissions between SDD and 30 days in the SDD cohort. Two were non-cardiovascular readmissions (Day 4 and Day 22), whilst one was a cardiovascular readmission (complete heart block requiring pacemaker, occurring on day 20). These are detailed further in Table 4.

There were 24 (14.8%) readmissions in the standard discharge pathway, of which 13 (8.0%) were cardiovascular whilst 11 (6.8%) were non-cardiovascular. Of the cardiovascular admissions, 1 (0.6%) was due to stroke, 1 (0.6%) was a vascular complication, whilst 6 (3.7%) were due to delayed pacemaker requirement (Table 3). There was no stroke, bleeding or vascular site complication up to 30 days in the SDD group. The median time to discharge in the standard discharge cohort was 3 (±2) days.

11.5 Discussion

This study found that 11.0% of the studied cohort were hypothetically eligible for SDD using the NSDST clinical pathway. There were no deaths in the SDD cohort, and no differences in rehospitalisation between discharge and 30-days when compared to the standard discharge cohort. Furthermore, the median time to discharge was 3 days in the standard discharge pathway, and there were no complications noted between Day 0 and Day 3 in any of the SDD

cohort to suggest additional benefit with standard discharge. The results suggest that within this selective low-risk TAVI cohort, SDD would have been safe and feasible using the NSDST clinical pathway. When comparing baseline characteristics, the SDD cohort had a greater proportion of women but otherwise there were no major differences in demographics, imaging or procedural characteristics.

From the 182 patients screened, 20 (11.0%) were deemed suitable for SDD using our NSDST pathway, which differs to other major published SDD studies. Barker et al. prospectively demonstrated safety of SDD in 5.9% of their cohort; whilst Krishnaswamy et al. retrospectively published safety of SDD in 22.0% during the COVID-19 pandemic. In our study, most exclusions for SDD occurred pre-procedurally (49.4%), then post-procedurally (43.8%) followed by 6.8% intra-procedurally. The most common exclusion reason was conduction-related (Figure 2), which occurred in in 80.9% and remains an obstacle for widespread adoption of SDD. One influential factor of our cohort was the *absence* of patients with a prior pacemaker which was mandated by the CONDUCT-TAVI protocol. In Barker et al.'s study, 32.3% of the SDD cohort had a pre-existing pacemaker, whilst 13.3% of the SDD cohort had a pacemaker in Krishnaswamy et al.'s cohort. Due to the high incidence of conduction abnormalities post TAVI, patients with a prior pacemaker are often the most ideal candidates for SDD.

Conduction abnormalities post TAVI are primarily attributed to the anatomical proximity of the aortic valve complex to the membranous septum which harbours the Bundle of His. Aside from atrioventricular block, persistent onset new LBBB occurs in 20.1% patients post TAVI(298) and greatly increases the risk of delayed onset atrioventricular block after TAVI, and thus patients with new onset LBBB were excluded from our SDD pathway. However, a

recent study showed the utility of post-TAVI invasive His-Ventricle (HV) interval >70 milliseconds to help further risk stratify those at highest risk of complete heart block after post-TAVI LBBB(40), which could be incorporated into future SDD pathways.

Similarly, the use of self-expanding valves is a well-documented independent procedural predictor of HGAVB(295), often resulting in exclusion from prior SDD studies. Prior studies conducted by Barker et al. and Krishnaswamy et al. used balloon expandable valves in 96.8% and 91.2% of their SDD cohorts respectively. However changes to deployment techniques, such as the adoption of the *cusp-overlap* technique(299) along with a trend towards higher depths of implantation, have resulted in a steady reduction in pacemaker rates with self-expanding platforms(62). An important and unique strength of this paper is the use of self-expandable valves in 65.3% of the total cohort, suggesting feasibility of SDD *irrespective* of the valve choice.

Notably, there was one cardiac re-hospitalisation in the SDD cohort which occurred on Day 20, relating to delayed onset complete heart block requiring PPM implantation. Importantly, this complication occurred well after the median discharge time (3 days), suggesting a *standard* admission would not have prevented rehospitalisation. Nevertheless, delayed conduction disease remains difficult to predict and is an important challenge for SDD after TAVI, particularly with self-expanding valves. As a result, the NSDST clinical pathway consists of relatively *conservative* ECG exclusion criteria, such as excluding all post TAVI first-degree AVB as well as *any* new bundle branch block. The incidence of delayed high-grade atrioventricular block is also not well understood, with a recent systematic review estimating incidence at 5.2%(300). Notably, our study patient with delayed PPM implantation

had a balloon-expandable valve and was diagnosed as having complete heart block remotely from her loop recorder home monitoring and contacted to present to hospital.

From a financial standpoint, it is estimated SDD could have enabled savings in our health district of up to $USD 8000 per patient, by preventing the median 3-night hospital admission ($USD 2670 per day). In this study cohort alone, SDD had a hypothetical cost-saving of $USD 160,000, as well as potentially allowing earlier treatment of 20 other patients due to additional bed availability. Prior Australian cost-effectiveness analyses on a low-risk TAVR cohort in 2021 have shown self-expanding valves to be economically dominant (compared to surgical aortic valve replacement), and balloon-expandable valves to be financially favourable, with an incremental cost-effectiveness ratio (ICER) of $AUD 3521 ($USD 2270) per quality adjusted life year compared to surgical aortic valve replacement(301). Incorporating same-day discharge would equate to considerable economic and clinical dominance of TAVR, irrespective of valve choice, as a treatment for aortic stenosis.

Limitations

As a retrospective sub-analysis of patients included in a separate prospective study cohort, our findings need dedicated and prospective validation. As a retrospective assessment, application of the North Shore clinical pathway was modified and approximated using clinical documentation, such as for mobility and vascular access site status, which may be prone to error. Furthermore, it must be noted that patients with a prior PPM were excluded from the original CONDUCT-TAVI study's cohort. Although in this case, this may mean the present study underestimates the actual proportion of patients suitable for SDD. A prospective study of the North Shore pathway in an all-comer population is warranted and currently underway (ACTRN12624000571572).

11.6 Conclusions

This study demonstrates that SDD after minimalist transfemoral TAVR can be safe and feasible in select low-risk patients, in both self-expanding and balloon-expandable valve cohorts. It also serves as a promising initial evaluation of the Australian derived North Shore Day Stay clinical pathway, which is currently undergoing prospective evaluation for use as a standardised protocol to guide SDD in clinical practice. SDD in selective patients may provide a strategy to streamline the accessibility of TAVR, improve hospital congestion and reduce costs amid growing demand for the procedure.

Funding

This is an investigator initiated and funded project. No external funding was sought. Dr. Rao is supported by a National Health and Medical Research Council (NHMRC) and Heart Research Australia Postgraduate Scholarship. Dr. Litkouhi is supported by a Heart Research Australia Project Grant.

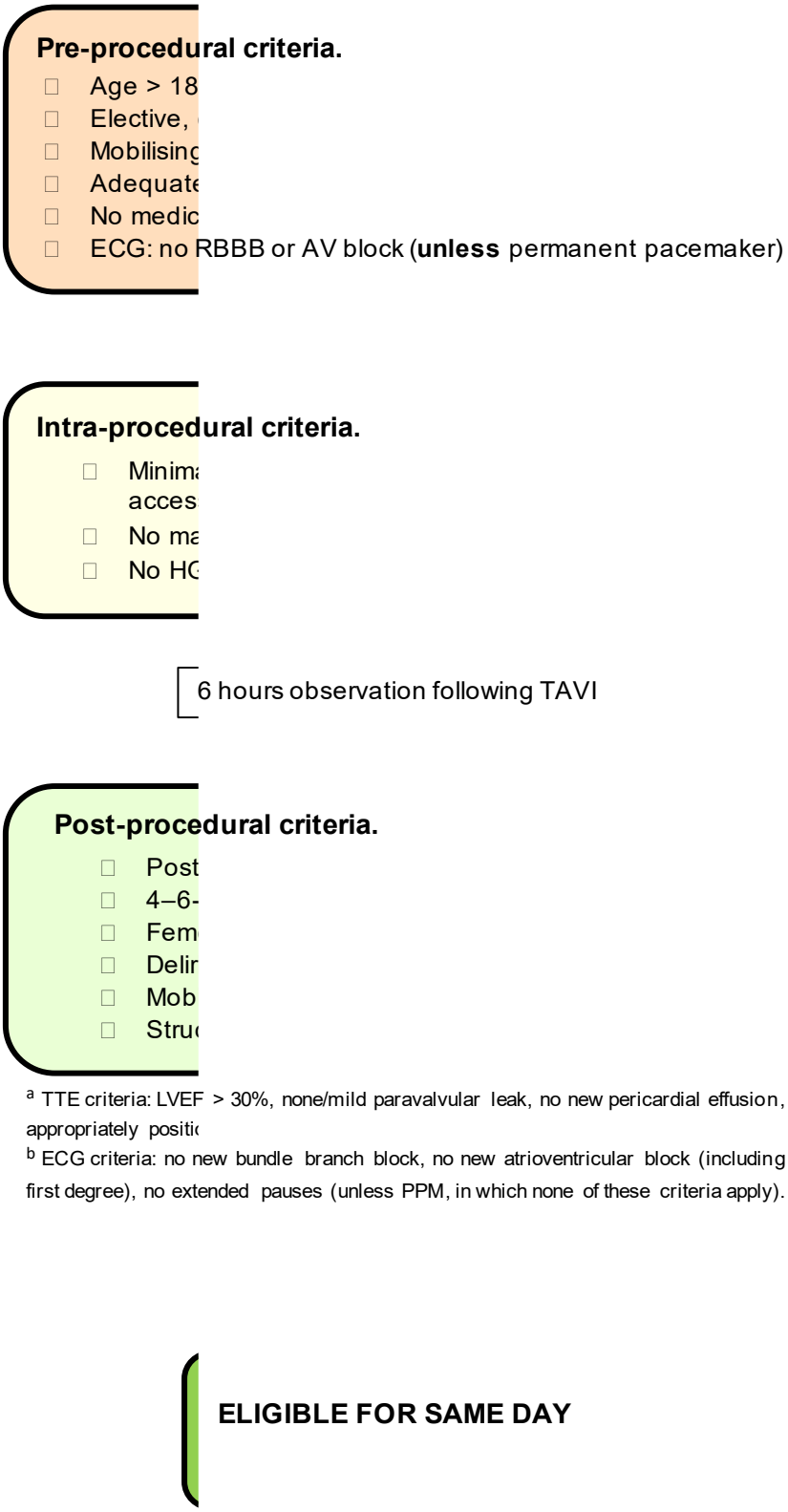
Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgements

Informed consent was obtained from all individual participants included in the study.

Figure 1: 'NORTH SHORE DAY STAY TAVI' clinical pathway for assessment of suitability for same day discharge after transcatheter aortic valve implantation.



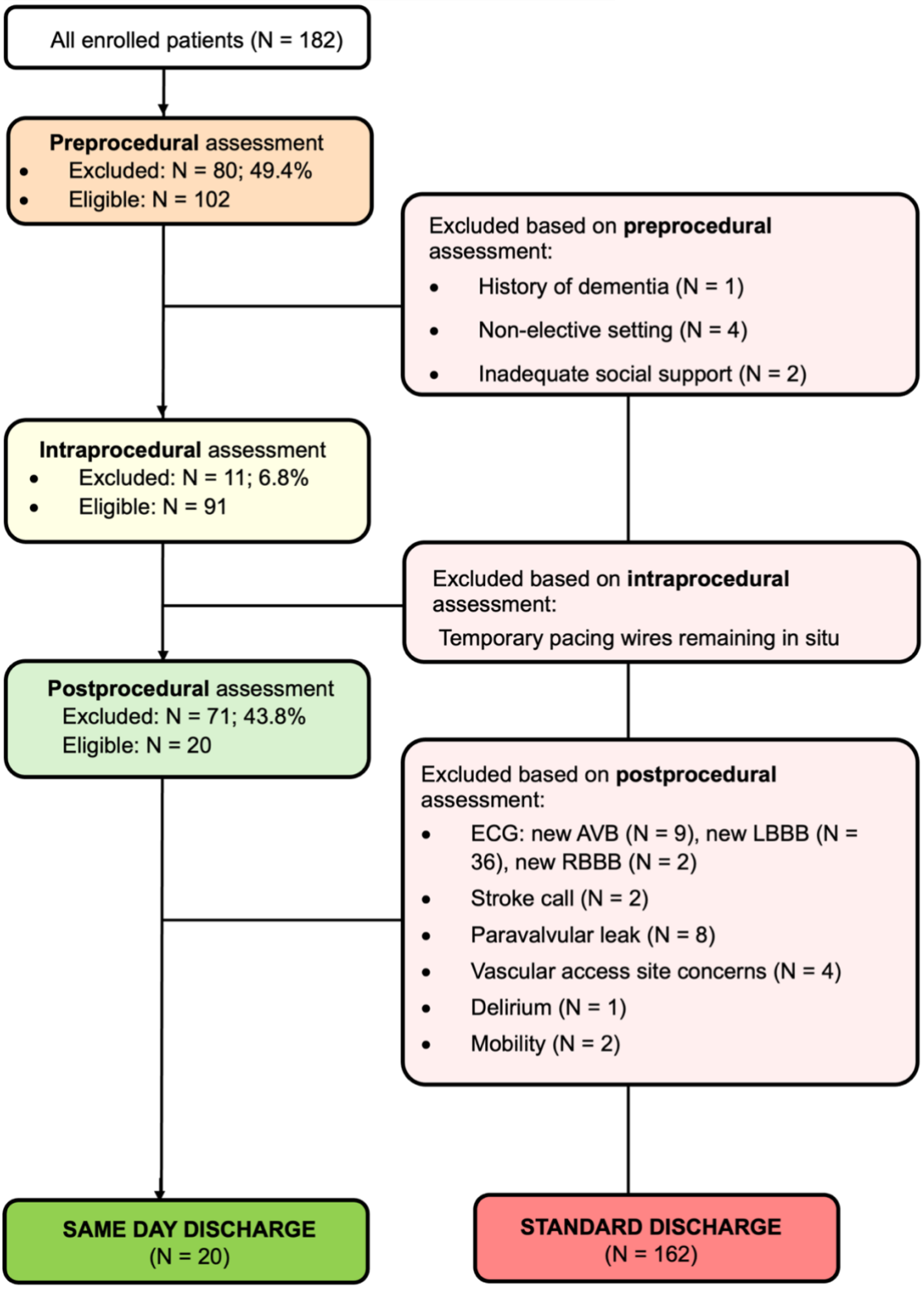
[a] TTE criteria: LVEF > 30%, none/mild paravalvular leak, no new pericardial effusion, appropriately positi

[b] ECG criteria: no new bundle branch block, no new atrioventricular block (including first degree), no extended pauses (unless PPM, in which none of these criteria apply).

Abbreviations: RBBB: right bundle branch block, AV: atrioventricular; HGAVB: high grade

atrioventricular block; PPM: permanent pacemaker.

Figure 2: Study flowchart



Abbreviations: AVB: atrioventricular block; LBBB: left bundle branch block; RBBB: right bundle branch block.

Results tables

Table 1: Baseline patient characteristics

	Same Day Discharge (n = 20)	Standard Discharge (n = 162)	*p*-value
Demographic Factors			
Age [mean, (SD)]	83.7 (6.7)	81.9 (6.4)	0.632
Sex (Female) [n (%)]	11 (55.0%)	51 (31.5%)	**0.036**
BMI [mean (SD)]	26.1 (5.0)	27.6 (5.4)	0.696
STS-PROM score [median, (IQR)]	3.1 (5.1)	2.5 (2.5)	0.140
Hypertension [n (%)]	16 (80.0%)	131 (80.9%)	0.926
Diabetes [n (%)]	4 (20.0%)	47 (29.0%)	0.397
Coronary Artery Disease [n (%)]	10 (50.0%)	51 (31.5%)	0.098
End-stage renal disease [n (%)]	1 (5.0%)	3 (1.9%)	0.368
Prior PCI [n (%)]	5 (25.0%)	42 (25.9%)	0.929
Prior CABG [n (%)]	2 (10.0%)	16 (9.9%)	0.986
Prior stroke [n (%)]	3 (15.0%)	13 (8.0%)	0.299
NYHA class (III or IV)	16 (80.0%)	136 (84.0%)	0.440
Mean aortic valve gradient (mmHg) (mean, SD)	42.9 (10.3)	45.1 (16.9)	0.278
Left ventricular ejection fraction (LVEF) (%) [mean (SD)]	59.0 (9.8)	58.7 (8.4)	0.912
Baseline ECG			
Atrial fibrillation [n (%)]	5 (25.0%)	22 (13.6%)	0.175
Sinus rhythm [n (%)]	13 (65.0%)	137 (84.6%)	**0.030**
First-degree AV block	0 (0%)	49 (30.2%)	-
Right bundle branch block [n (%)]	0 (0.0%)	31 (19.1%)	-
Left bundle branch block [n (%)]	1 (5.0%)	11 (6.8%)	0.761
Prior pacemaker [n (%)]	0 (0.0%)	0 (0.0%)	–

Abbreviations: BMI: body mass index; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; NYHA: New York Heart Association; AV: atrioventricular

Table 2: Procedural characteristics

	Same Day Discharge (n = 20)	Standard Discharge (n = 162)	*p*-value
Procedural characteristics			
Valve type, n (%) -Self-Expanding -Balloon-expandable	 10 (50.0%) 10 (50.0%)	 109 (67.3%) 53 (32.7%)	0.125
Membranous septum length (mm) [mean, SD]	3.7 (1.8)	3.3 (2.4)	0.269
Annular measurements [mean, SD] - Area - Perimeter	 454.2 (118.7) 76.2 (9.9)	 482.0 (101.3) 78.7 (8.2)	 0.258 0.201
Valve oversizing% [mean, SD]	15.0 (9.7)	16.5 (8.6)	0.244
Implantation depth (mm) [mean, SD]	3.3 (2.0)	3.6 (2.0)	0.276

Table 3: In hospital and 30-day mortality and morbidity outcomes for same day compared to standard discharge cohorts.

	Same Day Discharge (n = 20)	Standard Discharge (n = 162)	p-value
In Hospital Outcomes			
Mortality, n (%)	0 (0.0%)	1 (0.6%)	0.890
Stroke, n (%)	0 (0.0%)	6 (3.7%)	0.492
Major Bleeding, n (%)	0 (0.0%)	4 (2.5%)	0.625
Vascular complications, n (%)	0 (0.0%)	7 (4.3%)	0.436
Permanent pacemaker implantation, n (%)	0 (0.0%)	29 (17.9%)	0.039
Delirium, n (%)	0 (0.0%)	4 (2.5%)	0.625
Myocardial infarction, n (%)	0 (0.0%)	0 (0.0%)	
Median time to discharge, days (IQR)	n/a	3.0 (2)	
Discharge to 30 Day Outcomes			
Mortality, n (%)	0 (0.0%)	0 (0.0%)	
Hospital readmission, n (%)	3 (15.0%)	24 (14.8%)	0.510
Cardiovascular hospitalisation	*1 (5.0%)*	*13 (8.0%)*	*0.569*
Non cardiovascular hospitalisation	*2 (10.0%)*	*11 (6.8%)*	*0.346*
Stroke, n (%)	0 (0.0%)	1 (0.6%)	0.890
Bleeding, n (%)	0 (0.0%)	0 (0.0%)	
Vascular complications, n (%)	0 (0.0%)	1 (0.6%)	0.890

Permanent pacemaker implantation, n (%)	1 (5.0%)	6 (3.7%)	0.508
Delirium, n (%)	0 (0.0%)	0 (0.0%)	
Myocardial infarction, n (%)	0 (0.0%)	0 (0.0%)	

Table 4: Patients requiring any rehospitalisation in the SDD cohort (n=3)

#	Age (Gender)	BMI	STS %	Baseline bloods	Baseline TTE	Baseline ECG	Valve	Post-TAVI PVL	24 hr ECG	Readmission (days post TAVI)	Reason for rehospitalisation
1	72 (F)	24.9	1.37	Hb 118 Cr 105	Mean gradient 41mmHg LVEF 60%	SR PR: 140ms QRS: 68ms	BEV 20mm	Trivial	SR PR: 152ms QRS: 84ms	20	Complete heart block detected via loop recorder
2	73 (M)	16.3	1.32	Hb 144 Cr 73	Mean gradient 44mmHg LVEF 65%	AF QRS: 76	SEV 34mm	Mild	AF QRS: 84ms	4	Pneumonia
3	76 (F)	32.2	9.30	Hb 120 Cr 348	Mean gradient 28mmHg LVEF 60% *low SVI	AF QRS: 71	SEV 26mm	Trivial	AF QRS: 100ms	22	Pneumonia

*low SVI (stroke volume indexed) – i.e. patient had paradoxical low flow low gradient severe aortic stenosis

BMI: body mass index; STS: Society of Thoracic Surgery Risk score; TTE: transthoracic echocardiogram; PVL: paravalvular leak; TAVI; transcatheter aortic valve implantation; BEV: balloon expandable valve; SEV: self-expandable valve; Hb: haemoglobin; Cr: creatinine; AF: atrial fibrillation

CHAPTER 12: Recurrent valve frame infolding in the 34mm self-expanding Medtronic Evolut Pro Plus transcatheter valve system: a single centre experience

Heart, Lung and Circulation
Volume 32, Issue 12, December 2023, Pages 1482-1488

Original Article

Recurrent Valve Frame Infolding in the 34mm Self-Expanding Medtronic Evolut Pro+ Transcatheter Valve System: ASingle Centre Experience

Karan Rao MD, MPH [a b c], Alexandra Baer BSN, MSHM [b], Peter Hansen MBBS, PhD [a b], Ravinay Bhindi MBBS, PhD [a b c]

Published in:

Heart, Lung and Circulation 32 (12) Pages 1482-1488. DOI: 10.1016/j.hlc.2023.08.015

Author contribution statement:

This chapter is published work for which I was first author. I assisted in the design and conception of the study, and collected and analysed the data, interpreted the findings, and drafted the manuscript. Professor Ravinay Bhindi and co-authors provided intellectual input, critical revision, and final approval. I take primary responsibility for the accuracy and integrity of the work presented.

Recurrent valve frame infolding in the 34mm self-expanding Medtronic Evolut Pro+ transcatheter valve system, a single centre experience

Karan Rao[1, 2, 3], Alexandra Baer[2], Peter Hansen[1, 2.] & Ravinay Bhindi[1, 2, 3]

[1]Royal North Shore Hospital, Sydney, Australia
[2]North Shore Private Hospital, Sydney, Australia
[3]University of Sydney, Australia

Corresponding author
Professor Ravinay Bhindi
Royal North Shore Hospital, Reserve Road, St. Leonards, 2065
ravinay.bhindi@sydney.edu.au

Word Count: 2890 (includes figures, tables, references)

The authors do not have any disclosures.

This is an investigator-initiated study with no external funding.

12.1 Abstract

Background

Valve frame infolding (VFI) is a rare complication (1-3%) of transcatheter aortic valve implantation (TAVI), which primarily occurs in large sized self-expanding valves. We report the incidence of VFI in a small group of patients with highly calcified and extra-large aortic annuli, who underwent implantation of the newer generation 34mm Medtronic Evolut Pro+ (EP+) system.

Methods

A retrospective review was conducted on all patients presenting to an experienced TAVI centre in Sydney, Australia, between June and October 2022, for transfemoral TAVI using the Medtronic 34mm EP+ valve system. VFI was diagnosed using fluoroscopy, and pre-procedure computed tomography (CT) was analysed offline.

Results

VFI occurred in 4 of 10 patients who underwent TAVI using the 34mm EP+ system. Between VFI and non-VFI patients, the annular size, aortic angulation and total calcium volume was similar. Calcium distribution between the coronary cusps was symmetric in non-VFI patients (37%, 33% and 30%), compared to 52% in the non-coronary cusp (NCC) in VFI patients. The mean ellipticity index was higher in VFI vs. non-VFI (22% vs. 14%) patients.

Conclusion

The 34mm EP+ is vital for safe and effective treatment of a niche subgroup of patients with extra-large annuli and extensive calcification, however operators should be aware of the increased incidence of VFI. Heavy eccentric calcification at the NCC, as well as using the

cusp-overlap implant technique may exacerbate VFI, whilst multiplanar fluoroscopic screening may improve recognition.

12.2 Background

Transcatheter aortic valve implantation (TAVI) is a highly effective and minimally invasive treatment option for all patients with severe aortic stenosis(137, 138). The Medtronic Evolut Pro+ (EP+) system is a recent generation, self-expanding TAVI platform. Compared to prior generations, the EP+ system contains a porcine pericardial tissue wrap on the distal outer stent layer, which has been shown to reduce paravalvular leak (PVL) (302).

An infrequent, but potentially serious complication of self-expanding valve platforms is the threat of valve frame infolding (VFI), which is thought to occur in 1-3% of all cases(303, 304). VFI is distinct from valve under-expansion and occurs when the stent frame folds *inward* along the vertical axis away from the valve inflow. VFI may cause valvular aortic regurgitation, device nose-cone entrapment, as well as leaflet distortion and reduced durability.

A number of procedural factors such as larger self-expanding valve sizes, inadequate valve loading, lack of balloon pre-dilatation, and valve re-sheathing have been reported to precipitate VFI (305, 306). Patient anatomical factors such as eccentric calcification, a highly elliptical annulus, or bicuspid valve anatomy may also increase the risk(306).

This case series reports the incidence of VFI in all cases which used the 34mm Medtronic EP+ system at a single centre. The 34mm EP+ system helps to treat a unique patient population, with extra-large and heavily calcified aortic annuli, which may not be well-served well by other platforms. However, it is hypothesized that the incidence of VFI with the 34mm

EP+ system may be greater than in prior generations, secondary to the high-risk patient anatomy, as well as valve size and design.

12.3 Methods

A retrospective review was conducted on all patients presenting to an experienced TAVI centre in Sydney, Australia, between June and October 2022, for elective TAVI using the Medtronic 34mm EP+ valve system. Valve choice was based on Heart Team discretion and was based primarily on annular measurements and the presence of significant aortic valve apparatus calcification. Procedural characteristics, pre-procedure imaging, and haemodynamic outcomes were compared between patients with VFI against patients without VFI.

TAVI procedure

All TAVI procedures were elective and transfemoral, using conscious sedation. Two TAVI operators performed all procedures (RB and PH). All patients had primary femoral artery and secondary radial artery access, with a 6-French Pigtail catheter placed in the non-coronary cusp for aortography. The aortic valve was crossed with a straight-tip 0.035-inch guidewire (Cook Medical, Indiana, United States) and then exchanged for a double-curve Lunderquist wire (Cook Medical, Indiana, United States). The valve was fluoroscopically screened after preparation to ensure adequate loading. Fast left ventricular pacing was performed over the stiff left ventricle wire. Balloon pre-dilatation was *not* routinely performed, unless deemed necessary by the operators, as is usual practice at our centre. The valve was deployed using the *cusp overlap* technique, to achieve a higher implant and minimise pacemaker risk. After initial valve positioning in the two-cusp view, the three-cusp (LAO) view was routinely used to confirm implantation depth at the LCC. Further individual procedure comments for each patient can be found in Tables 1 and 2.

Diagnosis of VFI

Patient case data as well as the fluoroscopic images were thoroughly evaluated for evidence of VFI. Diagnosis of VFI was made fluoroscopically using either the "straight line distortion" or "string" sign suggesting an inward overlap of valve frame cells, or by noting an obviously reduced transverse valve diameter during partial or complete deployment.

Pre-procedure imaging

Individual patient anatomy was evaluated using routine pre-procedure computed tomography (CT) imaging. Offline measurements were performed on 3Mensio Medical Imaging (Pie Medical Imaging, Maastricht, Netherlands) to analyse annular geometry as well as aortic valve calcium volume and distribution. The annular ellipticity index was calculated as 1 – [minimum annular diameter / maximum annular diameter]. Calcium quantification was reported as a total volume (mm^3) and split by aortic cusp, using automatically derived and individualised Hounsfield Unit cut-offs. The area of analysis was between the sinotubular junction (STJ) down to the inferior margin of the LVOT. Finally, pre- and post-procedure transthoracic echocardiography was reviewed for haemodynamic evaluation.

12.4 Results

A total of 10 patients underwent elective transfemoral TAVI using the 34mm EP+ system between June and October 2022. Of that cohort, 4 patients had evidence of VFI. Three cases were diagnosed after partial deployment, after which the valve was recaptured, and a new valve was prepared and deployed. One case was diagnosed after complete deployment and balloon post-dilatation was performed to optimise valve symmetry.

The two groups (infolded and non-infolded) of patients had similar distribution in their annular size, aortic angulation, and calcium quantification (Table 3). However, calcium distribution was skewed in infolded patients, with 52% of the calcium volume located on the non-coronary cusp (NCC), compared to 28% on the right coronary cusp (RCC) and 20% on the left coronary cusp (LCC). The calcium in non-infolded patients was more evenly distributed, with 37% on the NCC, 30% in the RCC and 33% in the LCC (Figure 1). Further details on each case within the series can be found in Tables 1 and 2.

All four patients with diagnosed VFI had native tricuspid aortic valve anatomy, whilst two of the six patients without VFI had bicuspid anatomy. There was no major acute haemodynamic compromise in any of the patients, with adequate post procedure aortic valve gradients and no significant paravalvular leak.

12.5 Discussion

VFI is a potentially serious complication of self-expanding transcatheter valves, which may under-recognised and under-reported. VFI can lead to significant paravalvular or valvular regurgitation or the deployment of a sub-optimally expanded valve, which can affect leaflet function and durability. In this small case series of ten patients with highly calcified and large annuli which warranted the 34mm EP+ system, VFI occurred in four cases.

Potential contributors to VFI

The 34mm EP+ system is often reserved for highly calcified anatomies, with large annuli, where there is a greater fear of inadequate valve sealing and paravalvular leak, or annular rupture, using other valve systems. A systematic review of VFI cases from 2014-2020 found all occurred in self-expanding valves 29mm or larger (305). It has been proposed that generally in supra-annular tall frame devices, the radial strength during self-expansion is

inversely proportional to valve size, and thus the partially deployed inflow segment of the 34mm EP+ valve is at the highest risk of infolding.

Heavy calcification is proposed to be a risk factor for VFI; however, the role of calcium quantification and distribution is unclear. This case series, whilst small, demonstrated that both VFI and non-VFI groups had similarly heavy calcium volume in the device landing zone: 2383mm^3 vs 2399mm^3 respectively. However, the results raise the possibility that calcification eccentricity may be independently linked to VFI. In the VFI series (n=4), 52% of the calcium was located within the NCC, whilst the distribution was much more even in the non-VFI series.

The risk of VFI with eccentric NCC calcification may be compounded with the use of the *cusp overlap* technique(307). As unsheathing of the valve is commenced above the annular plane in the 2-cusp view, the initial deployment may increase exposure of the partially deployed valve frame to leaflet calcification.

Exacerbating this, the *cusp overlap* technique advocates the use of an extra-stiff double curve Lunderquist wire, which naturally biases towards the NCC. Whilst this wire provides greater precision with implantation depth, it inadvertently may increase the risk of the partially deployed valve frame to contact any eccentric NCC calcification.

Since any annuli which pose a high degree of constraint may increase the risk of VFI, annular ellipticity was hypothesized to be a plausible contributor. In this small cohort, the infolded patients had a greater mean ellipticity index (0.22), compared to non-infolded patients (0.14), however this did not reach statistical significance. Whilst definitive conclusions are limited

by the small sample size, a plausible explanation is that a highly elliptical annulus may result in relative oversizing at the minor axis, which may increase the risk of suboptimal expansion and VFI.

Bicuspid anatomy was not observed to be a key predictor, although this may be attributed to the small population. Bicuspid anatomy often leads to valve sizing challenges due to a large and irregularly shaped aortic valve apparatus, as well as heavy and eccentric calcification, and thus has been previously reported to be an important risk factor for VFI(305).

Prevention and Diagnosis

Adequate valve loading can help to prevent VFI and is confirmed on pre-deployment *ex vivo* valve fluoroscopic assessment, which should be performed using a magnified and high-resolution cine capture. A misload is diagnosed as inflow crown overlap extending further past the fourth node. If a misload is identified (Figure 2) the valve should not be used, and a second valve should be prepared. In this small case series, minor inflow crown overlap (less than four nodes) was not found to be a strong risk factor for subsequent VFI.

Balloon pre-dilatation prepares the aortic valve for passage of the delivery system, as well as adequate transcatheter expansion(308). Ancona et al.(305) in their systematic review suggest that a lack of pre-dilatation contributed to 16% of all cases of VFI. Whilst not performed in this case series, balloon pre-dilatation should be strongly considered in *all* patients undergoing TAVI with the 34mm EP+ system. Similarly, avoiding unnecessary valve re-sheathing may optimise the radial strength of the larger sized valves, and therefore also reduce the risk of VFI.

In real-world practice, early recognition of VFI can be challenging. On fluoroscopy, experienced operators may note a reduced transverse diameter of the partially deployed segment of the self-expanding valve. Otherwise, inward stent cell overlap may be seen as the "string sign" which refers to an abnormal vertical line seen on a two-dimensional fluoroscopic plane (Figure 3). Certain fluoroscopic angles, such as the right anterior oblique (RAO) and caudal projection may mask VFI, and thus multiplanar imaging is highly recommended.

Treatment

If VFI is recognised early, it is recommended that the valve is re-captured, and a new valve is prepared and deployed. This is recommended to prevent the risk of nose cone entrapment which may occur if an infolded valve is deployed. Figure 4 shows an infolded valve which was recaptured.

If VFI is diagnosed following final deployment, post-dilatation is recommended to restore symmetry and resolve any sudden paravalvular regurgitation. It should be noted, that poorly expanded or infolded valves, especially with a shallow depth of implant, are at a higher risk of valve embolization. Furthermore, care also needs to be taken when removing the nose cone to in this setting to avoid device embolization. It is also important not to remove the LV guidewire until VFI has been excluded, otherwise operators may unintentionally re-cross the aortic valve outside the infolded prosthesis.

12.6 Conclusion

VFI is an important complication of self-expanding transcatheter valves and is mostly observed with large valve sizes due to reduced radial tension during early deployment. In this small case series of 10 consecutive patients with large annuli and extensive aortic calcification, the Medtronic 34mm EP+ system infolded in 4 patients.

Heavy eccentric calcification at the NCC, as well as the use of the *cusp overlap* technique may exacerbate the likelihood of VFI, whilst meticulous multiplanar fluoroscopic imaging can improve its identification. Operators can mitigate the risk of VFI with careful valve loading, adequate pre-dilatation, and avoiding unnecessary re-sheathing. Treatment of VFI involves the recapture and deployment of a second device, or if already implanted, to post-dilate the infolded segment and restore symmetry.

The 34mm EP+ system facilitates the safe and efficacious treatment of patients with aortic stenosis with extra-large annuli and extensive calcification, a subgroup of patients that cannot be treated with alternative platforms. It is important however, for operators to be aware of VFI in cases using the Medtronic 34mm EP+ system.

12.7 Tables and Figures

Table 1: Patients with VFI (n=4)

Patient # (Age)	1	2	3	4
Age (years)	76	93	82	93
STS-PROM%	2.7	4.1	2.3	3.8
Access	Transfemoral	Transfemoral	Transfemoral	Transfemoral
Anaesthetic	Local, sedation	Local, sedation	Local, sedation	Local, sedation
Valve	Medtronic Evolute Pro Plus 34mm	Medtronic Evolute Pro Plus 34mm	Medtronic Evolute Pro Plus 34mm	Medtronic Evolute Pro Plus 34mm
Pacing	Via stiff LV wire	Via stiff LV wire	Via stiff LV wire	Via stiff LV wire
Pre dilatation	No	Yes 18mmx4.5cm True Dilatation Balloon (Bard)	No	No
Post dilatation	No	No	Yes 20mm True Dilatation Balloon	No
Ex-vivo screening of inflow crown (# of nodes) *Up to 4 nodes acceptable	3	1	2	2
Total number of valves used	2	2	1	2
Annular measurements Area (mm2) Perimeter (mm) Min. diameter (mm) Max. diameter (mm)	 645 91 23.5 33.1	 503 89 26.3 31.5	 588 88 23.6 31.1	 521 82 23.6 28.8
Ellipticity Index Ellipse minor axis	0.29 RCC	0.17 RCC	0.24 RCC	0.18 RCC
Calcium Total (mm3) NCC (mm3) RCC (mm3) LCC (mm3)	 2219 1467 (66.1%) 614 (27.7%) 138 (6.2%)	 1842 782 (42.5%) 482 (26.2%) 579 (31.4%)	 4354 2094(48.1%) 1129 (25.9%) 1132 (26.0%)	 1116 579 (51.9%) 347 (31.1%) 189 (16.9%)
Aortic angulation (degrees)	66	73	53	43
Pre-procedure Echo Peak gradient (mmHg) Mn gradient (mmHg) Aortic regurgitation	 53 33 Trivial	 74 42 Trivial	 91 57 Mild	 56 33 Mild
Post-procedure echo Peak Mn Aortic regurgitation	 8 5 Mild	 4 2 Trivial	 19 11 Mild-moderate	 6 3 Trivial

Abbreviations: STS-PROM - Society of Thoracic Surgeons – Predicted Risk of Mortality; NCC – non-coronary cusp; RCC – right coronary cusp; LCC – left coronary cusp

Table 2: Patients without VFI (n=6)

Patient# (Age)	1	2	3	4	5	6
Age	81	75	76	85	86	75
STS-PROM%	1.7	1.3	4.0	4.4	3.1	2.4

Access	Transfemoral	Transfemoral	Transfemoral	Transfemoral	Transfemoral	Transfemoral
Anaesthetic	Local, sedation	Local, sedation	Local, sedation	Local, sedation	Local, sedation	Local, sedation
Valve	Medtronic Evolute Pro Plus 34mm	Medtronic Evolute Pro Plus 34mm	Medtronic Evolute Pro Plus 34mm	Medtronic Evolute Pro Plus 34mm	Medtronic Evolute Pro Plus 34mm	Medtronic Evolute Pro Plus 34mm
Pacing	Via stiff LV wire	Via stiff LV wire	Via stiff LV wire	Via stiff LV wire	Via stiff LV wire	Via stiff LV wire
Pre dilatation	No	No	No	No	No	No
Post dilatation	No	No	No	No	No	No
Ex-vivo screening of inflow crown overlap (# of nodes) *Up to 4 nodes acceptable	1	1	0	2	1	2
Total number of valves used	1	1	1	1	1	1
Annular measurement Area (mm2) Perimeter (mm) Min. diameter (mm) Max. diameter (mm)	 582 87 25.4 29.2	 596 87 26.6 28.8	 582 87 24.4 30.4	 612 90 23.3 31.0	 677 92 28.4 27.5	 584 87 23.5 27.5
Ellipticity Index Ellipse minor axis	0.13 RCC	0.08 N/A	0.20 RCC	0.25 NCC	0.05 N/A	0.15 RCC
Cusps	Bicuspid (Sievers 1a, L/R fusion)	Bicuspid (Sievers 1a, L/R fusion)	Tricuspid	Tricuspid	Tricuspid	Tricuspid
Calcium: Total (mm3) NCC (mm3) RCC (mm3) LCC (mm3)	 1764 381 (21.6%) 265 (15.0%) 1119 (63.4%)	 2238 786 (35.1%) 848 (37.9%) 605 (27.0%)	 1684 492 (29.2%) 472 (28.0%) 720 (42.8%)	 3459 1429 (41.3%) 1362 (39.4%) 668(19.3%)	 3112 1826 (58.7%) 613 (19.7%) 674 (21.7%)	 2135 453 (21.2%) 752 (35.2%) 930 (43.3%)
Aortic angulation (degrees)	64	69	44	52	79	49
Pre-procedure echocardiogram Peak gradient (mmHg) Mean gradient (mmHg) Aortic regurgitation	 53 33 Trivial	 74 42 Trivial	 91 57 Mild	 56 33 Mild	 96 56 Mild	 92 57 Trivial
Post-procedure echocardiogram Peak Gradient (mmHg) Mean Gradient (mmHg) Aortic regurgitation	 12 6 Nil	 4 2 Trivial	 19 11 Mild-moderate	 6 3 Trivial	 23 11 Mild-moderate	 12 6 Trivial

Abbreviations: STS-PROM - Society of Thoracic Surgeons – Predicted Risk of Mortality; NCC – non-coronary cusp; RCC – right coronary cusp; LCC – left coronary cusp

Table 3: Comparison of key CT and transthoracic echocardiographic characteristics

Characteristic	Infolded (n=4)	Non-infolded (n=6)
Age (mean) (years)	86.0	79.7
Gender, male (%)	4 (100)	6 (100)
STS-PROM % (mean)	3.2	2.8
Annular measurements Area (mean) Perimeter (mean)	 564.3mm2 87.4mm	 605.6mm2 88.3mm
Ellipticity Index (mean)	0.22	0.14

Valve cusps Tricuspid Bicuspid	 4 0	 4 2
Total calcium (mean, mm^3) NCC (mean) RCC (mean) LCC (mean)	2382.8 1230.5 (52%) 643.0 (27%) 478.3 (20%)	2398.7 894.5 (37%) 718.7 (30%) 786 (33%)
Pre procedure echocardiogram Peak gradient (mean) Mean gradient (mean) >mild aortic regurgitation	 68.5 41.3 1/4	 77.0 46.3 0/6
Post procedure echocardiogram Peak gradient Mean gradient >mild aortic regurgitation	 9.3 5.3 1/4	 12.7 6.5 2/6

Abbreviations: STS-PROM - Society of Thoracic Surgeons – Predicted Risk of Mortality; NCC – non-coronary cusp; RCC – right coronary cusp; LCC – left coronary cusp

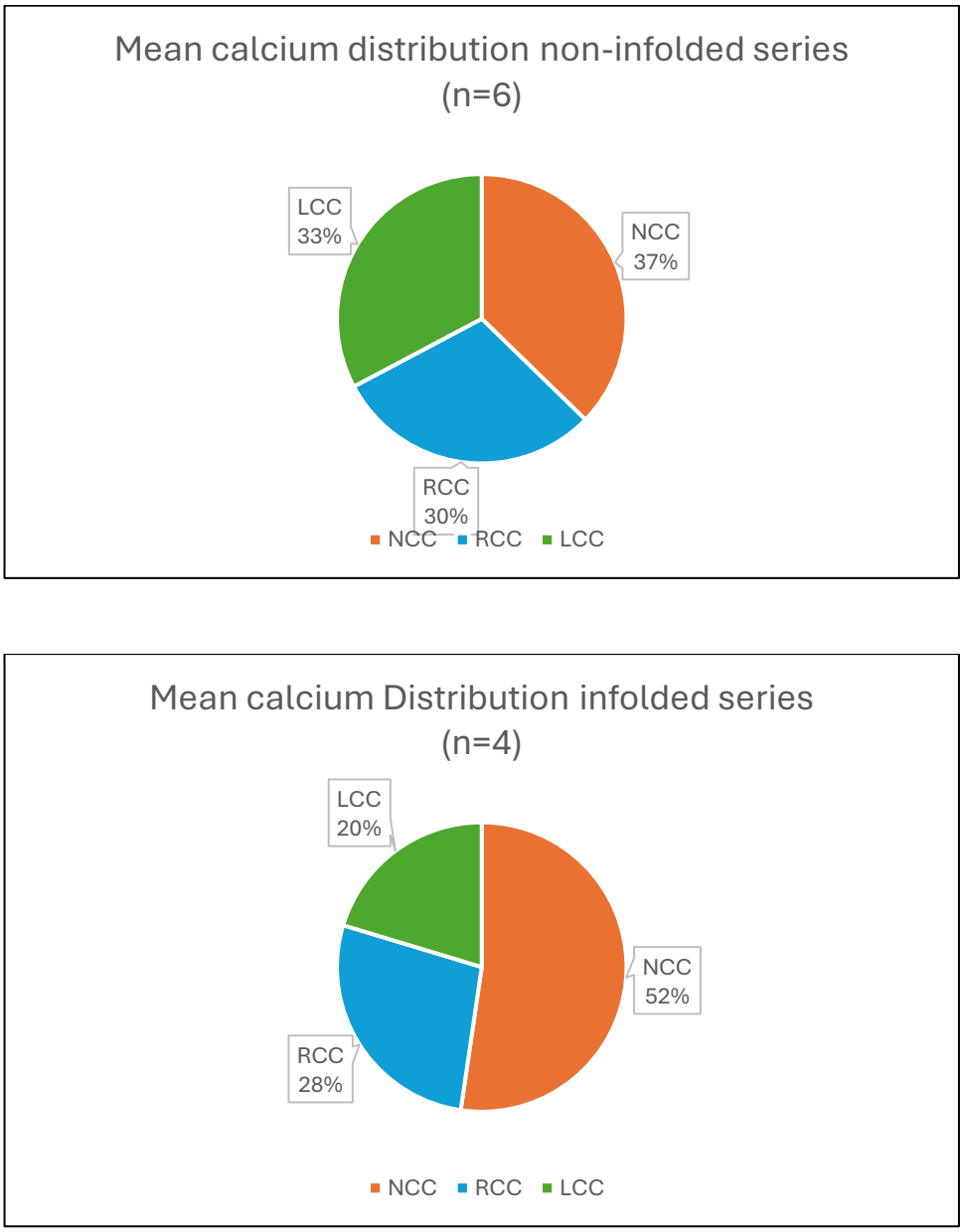


Figure 1: Comparison of mean calcium distribution across each aortic cusp in the infolded and non-infolded cases

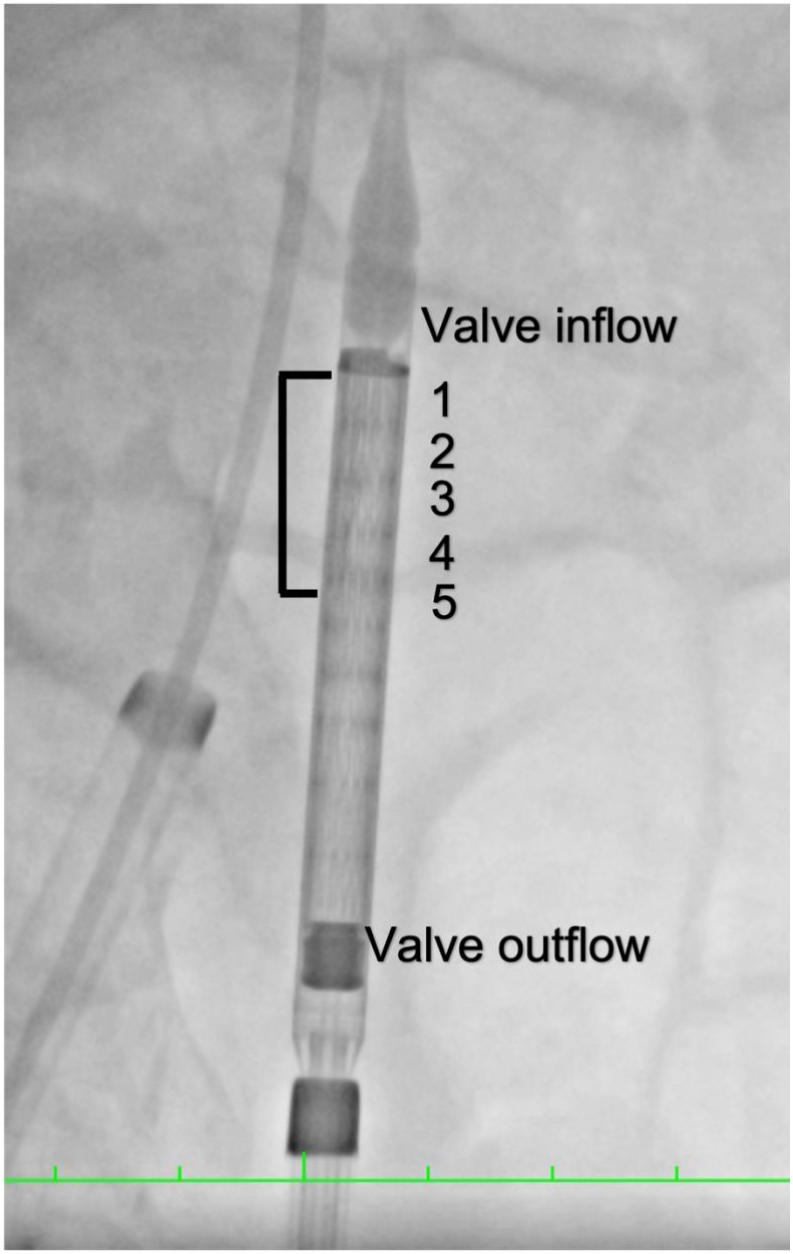


Figure 2: Example of a misload of the 34mm EP+ system, with a non-uniform shadow or line seen from the inflow segment extending below 4 nodes

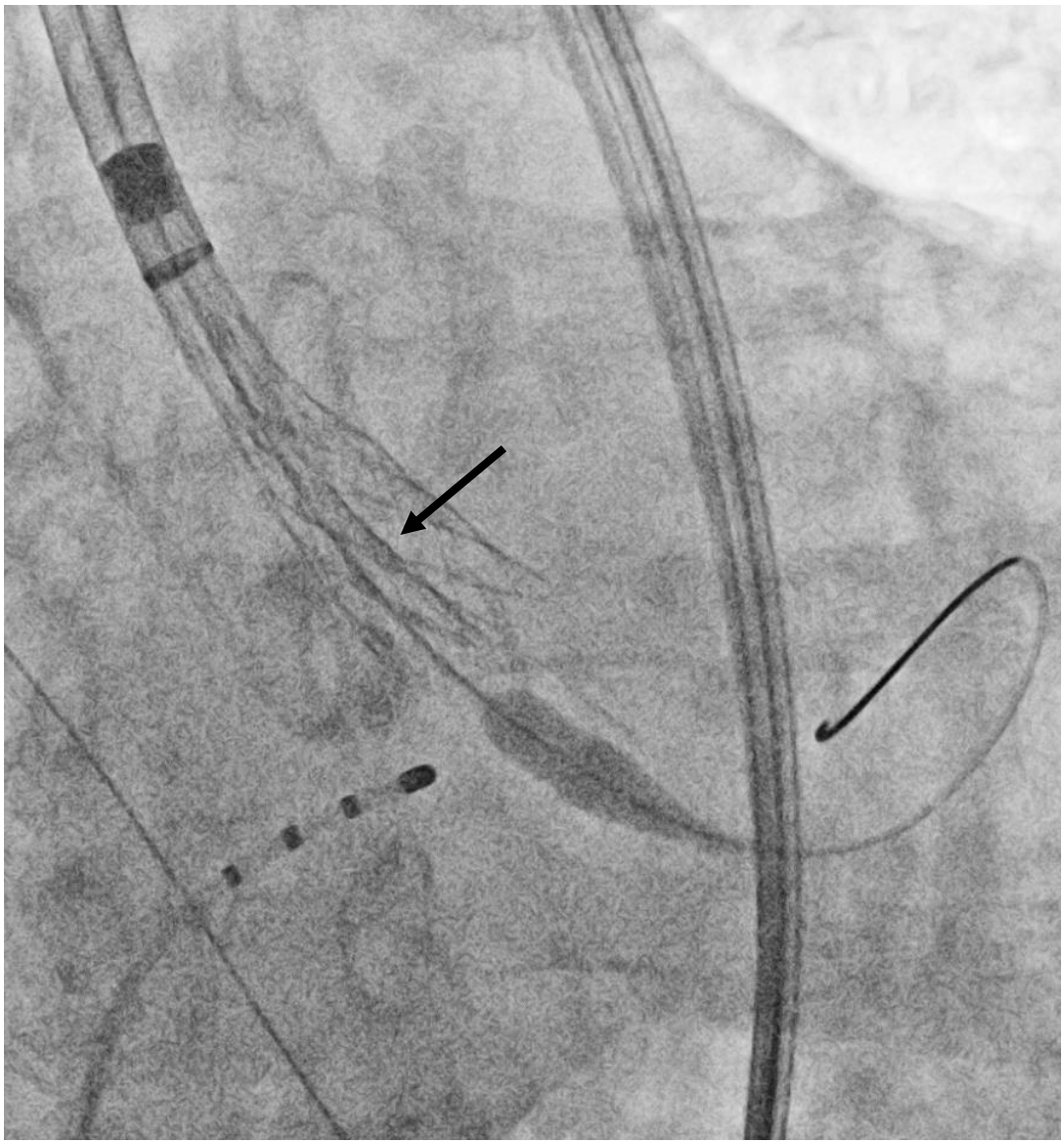


Figure 3: Vertical line or “string sign” seen on fluoroscopy, showing infolded segment of partially deployed 34mm EP+ valve.

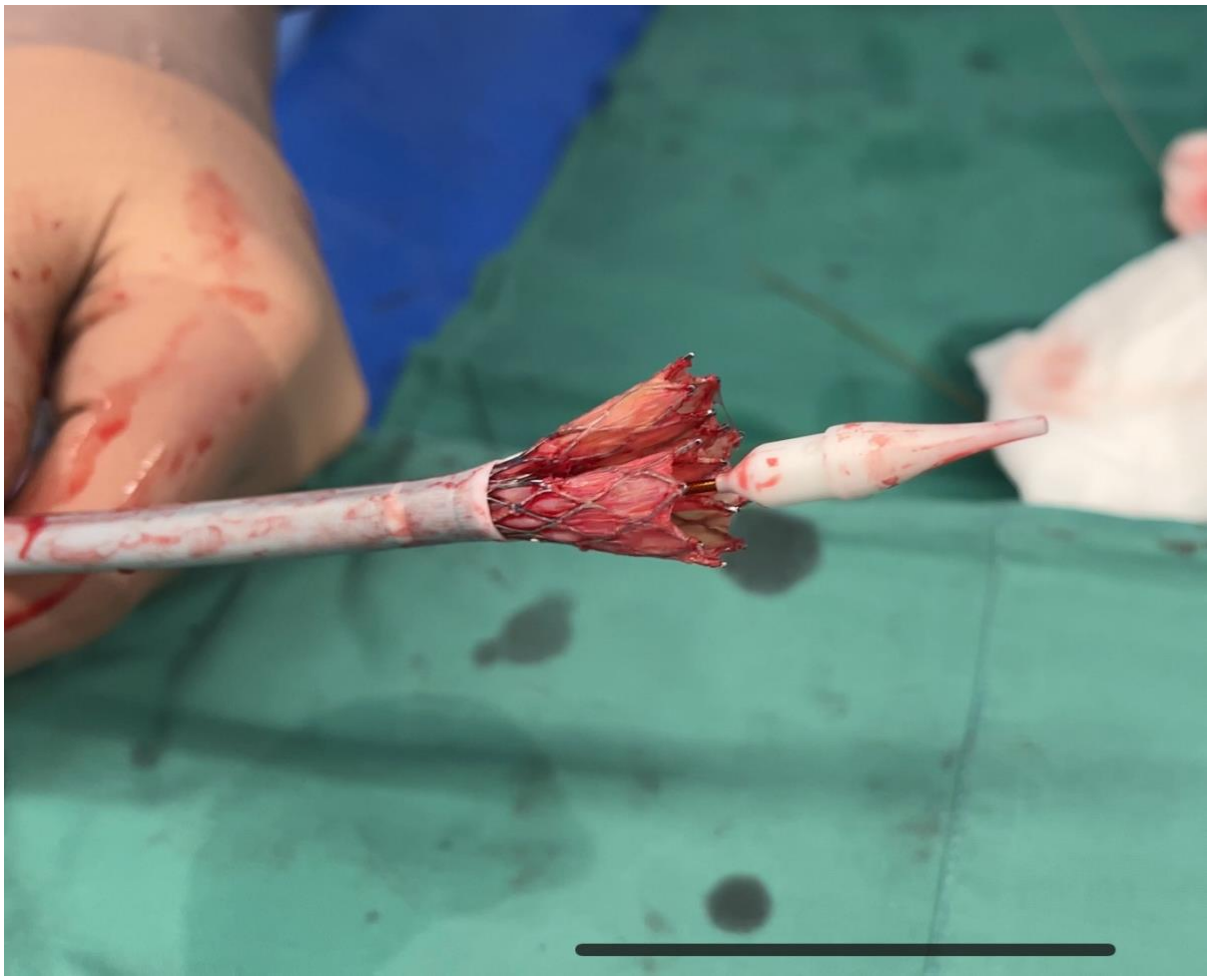


Figure 4: Close up image of an infolded 34mm EP+ valve which was recaptured.

SECTION V: DISCUSSION AND CONCLUSIONS

Over the past two decades, transcatheter aortic valve implantation (TAVI) has evolved into a safe and highly effective treatment for severe aortic stenosis. Nevertheless, conduction disturbances remain among the most common post-procedural complications and carry important implications for both short- and long-term morbidity and mortality. The primary aim of this thesis was to define the temporal incidence and determinants of high-grade atrioventricular block requiring new permanent pacemaker implantation (PPMI) following TAVI. Secondary aims included evaluating the incidence and prognostic significance of new, persistent left bundle branch block (LBBB) and to characterise the occurrence and predictors of new-onset atrial fibrillation (NOAF). Leveraging a rigorously monitored, large prospective cohort and integrating demographic, clinical, anatomical, electrophysiological, and procedural variables, this work delineates key drivers of post-TAVI conduction disease, proposes pragmatic risk-stratification tools, and outlines clinical care pathways to inform peri-procedural decision-making and follow-up.

Additionally, this thesis addresses broader procedural and management considerations pertinent to TAVI in 2025 and beyond, with a particular focus on lifetime management as indications extend to younger, lower-risk patients with longer life expectancy. These insights provide a framework to future-proof care and support personalized, long-term management strategies. Finally, the safety and feasibility of same-day discharge are also evaluated, reflecting a priority within contemporary TAVI pathways. Streamlined discharge protocols have the potential to relieve pressure on constrained public hospital systems while safely expanding access to this treatment.

Incidence and predictors of high-grade atrioventricular block resulting in a pacemaker implantation after TAVI

A key priority of this thesis was to accurately report the incidence of all clinically relevant

high-grade atrioventricular block resulting in a new PPMI at 1-year after TAVI. In our retrospective evaluation of 699 patients (Chapter 5) from our local institution, we report the 1-year incidence of new PPMI to be 14.6%. However, in our comprehensive prospective assessment of 200 patients (CONDUCT-TAVI – Chapter 6) the incidence was notably higher at 21.0%. We attribute this to a greater capture of subclinical and delayed events through implanted loop-recorder monitoring in the CONDUCT-TAVI cohort. Taken together, these findings indicate a persistently high burden of PPMI despite the adoption of contemporary valve platforms and refined implantation techniques, reiterating the need for better prediction and prevention strategies.

Another key contribution of this thesis is the detailed characterisation of delayed high-grade AV block, which was defined as occurring after 48 hours. Our published systematic review (Chapter 3) highlights the substantial heterogeneity in currently published rates, ranging between 1.7–14.6%, underscoring a need for focussed evaluation. In our retrospective work, which relied on review of the patient medical record, the incidence of a new delayed pacemaker requirement was 2.1% (Chapter 5). However, in CONDUCT-TAVI (Chapter 6), which employed continuous rhythm monitoring for 1-year, we report the incidence of delayed pacemaker requirement to be 7.5%. These findings highlight the systematic underestimation of late arrhythmic events through clinical follow-up alone, and support more proactive, prolonged post-procedural monitoring in select patients following TAVI.

With respect to risk prediction, our prospective study (Chapter 6) identified three key electrophysiological variables – baseline right bundle branch block (RBBB), an increase in the His-Ventricular (HV) interval (pre and post TAVI), and the inducibility of Mobitz type I block with rapid atrial pacing – as independent predictors of high-grade atrioventricular

block. To our knowledge, CONDUCT-TAVI represents the largest multimodal study addressing this issue, and offers a crucial advantage over other studies to date by examining all key risk factors simultaneously, thereby accounting for confounding. Anatomical and procedural factors, such as short membranous septum length, significant valve oversizing and implant depths exceeding the membranous septum, were predictive on univariable analysis but did not remain independent on multivariable modelling. However, post-hoc analyses of pre-procedural CT aortography in the CONDUCT-TAVI cohort (Chapter 7) identified that non-invasive anatomical prediction could be improved via integration of cardiac phase-specific three-dimensional CT aortography as well as the circumferential orientation of the conduction system – which has not been reported previously. Separately, we identified that diastolic-gated (as opposed to systolic-gated) measurements of the conduction system may better represent post-procedure pacemaker risk, which has also not been reported previously. Following prospective validation, the risk algorithms proposed in this thesis can be incorporated into pre-procedural TAVI planning to improve the prediction of high-grade atrioventricular block leading to PPMI after TAVI.

Natural history of post-TAVI conduction disease and recovery

New LBBB occurs frequently after TAVI, due to the exposed left bundle branch on the septal aspect of the left ventricular outflow tract. Through both our retrospective (Chapter 5) and prospective (Chapter 6) work, we demonstrate that whilst LBBB is common immediately following TAVI, roughly half will recover completely by 24 hours. However, in those with persistent LBBB, our published systematic review (Chapter 4) highlights the adverse implications on long-term mortality, heart-failure rehospitalisation and pacemaker requirement. We also report that whilst a new persistent right bundle branch block (RBBB) is less common after TAVI, it may carry an even greater impact on delayed pacemaker

requirement. These results indicate that whilst a substantial proportion of new bundle branch block after TAVI may recover, in those which it remains persistent, is not benign and has measurable prognostic implications.

Incidence and prediction of new-onset atrial fibrillation after TAVI

As a secondary outcome of CONDUCT-TAVI (Chapter 6), we report the incidence of new-onset atrial fibrillation (NOAF) to be 21.7% of AF-naïve patients, a higher rate than previously reported and likely explained by detection of subclinical episodes (via implantable loop recorder monitoring). The clinical significance of device-detected AF after TAVI though remains to be established in this potentially higher risk population and is a direction of future work. The outcomes of the ongoing randomised NOTION-4 study may offer some valuable insights(220) into the role of empiric anticoagulation post-TAVI. This randomised study aims to evaluate the effects of three months of standard anticoagulation (vs. single antiplatelet therapy) following TAVI, focusing on hypoattenuated leaflet thrombosis (HALT) and the incidence of ischemic stroke.

The prediction of NOAF after TAVI was observed to be more challenging compared to high-grade atrioventricular block, although the studies included in this thesis were primarily designed and to evaluate the latter. Whilst the results of our post-hoc analyses (Chapter 8) suggest that a pre-existing LBBB and rapid atrial pacing-induced AV Wenckebach are associated with increased risk of NOAF, the absence of a strong unifying risk signal likely reflects a combination of an underpowered secondary analysis, and the multifactorial aetiology of NOAF after TAVI. A promising and hypothesis-generating finding was the incorporation and utility of artificial intelligence-assisted computed tomography analysis. Through semi-automated chamber segmentation and statistical shape modelling analyses, we

demonstrated the feasibility of left atrial geometry, and subtle variations in the lateral and roof regions of the LA, as a novel predictive marker for NOAF after TAVI. By integrating semi-automation of chamber segmentation of routine CT into existing clinical workflows, clinicians could improve early risk stratification and further personalise post-TAVI surveillance protocols.

Practical clinical application and care pathways

The CONDUCT-TAVI PPM Score (Chapter 6) derived from prospective electrophysiology-centred data, provides a pragmatic rule-out tool for clinically significant high-grade atrioventricular block after TAVI. A key future application of this algorithm may lie in periprocedural stratification and identifying low-risk patients who could be considered for early or same-day discharge after TAVI. However external validation in independent cohorts is the next essential step before widespread adoption.

Secondarily, given that the CONDUCT-TAVI Score requires invasive electrophysiology studies – entailing additional cost, time and expertise – we conducted a post-hoc analysis centred on non-invasive anatomical and procedural predictors (Chapter 7). This refined algorithm incorporated more detailed anatomical characterisation to improve predictive accuracy. If validated in large prospective cohorts, this may offer a streamlined approach to estimating pacemaker risk, which betters currently existing risk scores, and utilises only standard pre-TAVI investigations.

The improved prediction of conduction outcomes enables early risk stratification for rapid post-procedural discharge, which can accelerate recovery and improve procedural efficiency. The North Shore Day-Stay TAVI (NSDST) pathway (Chapter 11) applies non-invasive

criteria to identify candidates for same-day discharge. Retrospective application to the CONDUCT-TAVI cohort suggested feasibility in 11.0%, and the pathway is therefore now undergoing prospective validation. If confirmed, the NSDST could streamline care and reduce costs by approximately USD $8000 (~$AUD 12200) per patient.

Role of refined CT-based anatomical evaluation in TAVI

Detailed CT-based anatomical assessment is integral to optimise index valve type, size and haemodynamics; as well as reduce the risk of coronary and structural complications. As discussed earlier, our work has helped to characterise the influence of the membranous septum and refine its predictive ability through incorporating measurements across the cardiac cycle, as well as its circumferential orientation.

Furthermore, in our *Expert Review* (Chapter 10), we explored the importance of CT-based anatomical evaluation in predicting feasibility of future valve-in-valve interventions, particularly as TAVI is increasingly being used to treat younger patients with longer life expectancy.

Limitations

Whilst the detailed and specific limitations of each study is included within its relevant chapter, there are some overarching limitations that should be addressed. Firstly, the prospective studies and subsequent post-hoc analyses were derived from a single campus (institute), which may introduce institutional bias and limit the generalisability of the findings. Secondly, considering arrhythmia outcomes were assessed up to one year, it is possible that some events were unrelated to the TAVI procedure itself, instead reflecting pre-existing or progressive degenerative conduction disease. Finally, the clinical implications of

subclinical (asymptomatic) high-grade atrioventricular block and new-onset atrial fibrillation has not been well characterised in a post-TAVI cohort and was not within the scope of this thesis but serves as another area for future research.

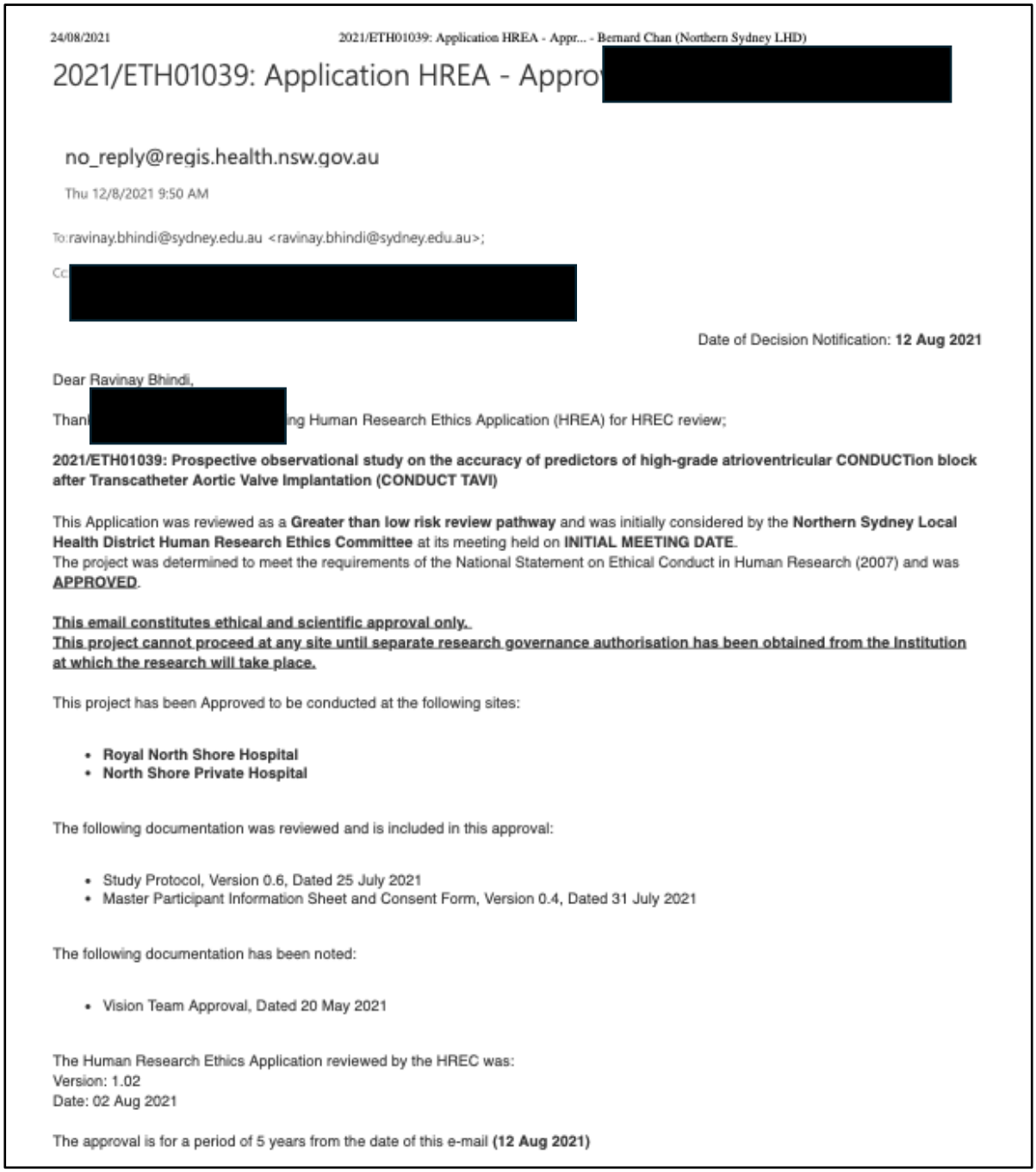
Summary and conclusions

Together, these findings contribute to the continued evolution of TAVI, from its inception where it was once a "one-size-fits-all" tool for inoperable patients, to the present, where it has become a nuanced, evidence-based and patient-centred long-term treatment strategy for patients of all surgical risk. By integrating targeted electrophysiological testing, personalised and semi-automated imaging, as well as robust predictive modelling, we can refine risk stratification, individualise follow-up protocols, and thereby improve long-term outcomes. This thesis lays the groundwork for future research aimed at prospectively validating these predictive tools in larger, multicentre cohorts, and integrating them into real-world clinical algorithms.

In conclusion, conduction disturbances after TAVI remain frequent, clinically consequential and mechanistically multifactorial, warranting precise strategies for risk stratification, surveillance, and long-term management. As TAVI continues to mature, the insights from this thesis outline actionable pathways to safer, more efficient, and personalised care.

SECTION VI: APPENDIX

A1: Relevant Ethics Approvals and Patient Information Consent Forms



24/08/2021 2021/ETH01039: Application HREA - Appr... - Bernard Chan (Northern Sydney LHD)

2021/ETH01039: Application HREA - Appro[redacted]

no_reply@regis.health.nsw.gov.au

Thu 12/8/2021 9:50 AM

To: ravinay.bhindi@sydney.edu.au <ravinay.bhindi@sydney.edu.au>;

Cc: [redacted]

Date of Decision Notification: **12 Aug 2021**

Dear Ravinay Bhindi,

Than[redacted]ing Human Research Ethics Application (HREA) for HREC review;

2021/ETH01039: Prospective observational study on the accuracy of predictors of high-grade atrioventricular CONDUCTion block after Transcatheter Aortic Valve Implantation (CONDUCT TAVI)

This Application was reviewed as a **Greater than low risk review pathway** and was initially considered by the **Northern Sydney Local Health District Human Research Ethics Committee** at its meeting held on **INITIAL MEETING DATE**.
The project was determined to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was **APPROVED**.

This email constitutes ethical and scientific approval only.
This project cannot proceed at any site until separate research governance authorisation has been obtained from the Institution at which the research will take place.

This project has been Approved to be conducted at the following sites:

- **Royal North Shore Hospital**
- **North Shore Private Hospital**

The following documentation was reviewed and is included in this approval:

- Study Protocol, Version 0.6, Dated 25 July 2021
- Master Participant Information Sheet and Consent Form, Version 0.4, Dated 31 July 2021

The following documentation has been noted:

- Vision Team Approval, Dated 20 May 2021

The Human Research Ethics Application reviewed by the HREC was:
Version: 1.02
Date: 02 Aug 2021

The approval is for a period of 5 years from the date of this e-mail **(12 Aug 2021)**

[redacted]

FW: 2024/ETH00727: Application HREA - Approved

1 message

[redacted]

[redacted]

Subject: 2024/ETH00727: Application HREA - Approved

Date of Decision Notification: **21 May 2024**

Dear [redacted]
Thank you for submitting the following Human Research Ethics Application (HREA) for HREC review;

2024/ETH00727: North Shore: Prediction of early pacemaker (PPM) requirement following transcatheter aortic valve implantation (North Shore Predict PPM TAVI)

This Application was reviewed as a **Greater than low risk review pathway** and was initially considered by the **Northern Sydney Local Health District Human Research Ethics Committee** at its meeting held on **ENTER INITIAL MEETING DATE**.
The project was determined to meet the requirements of the National Statement on Ethical Conduct in Human Research (2023) and was **APPROVED**.

This email constitutes ethical and scientific approval only.
This project cannot proceed at any site until separate research governance authorisation has been obtained from the Institution at which the research will take place.

This project has been Approved to be conducted at the following sites:

- **Royal North Shore Hospital**
- **North Shore Private Hospital**

The following documentation was reviewed and is included in this approval:

- HREA - 1.03 - 21/5/24
- Protocol - 1.1 - 21/5/24
- Waiver of Consent - 21/5/24
- CPI CV
- Site CPI form

Application Documents - (link will only be active for 14 days from the decision date. The approved documents are also available to download from forms section of this project in REGIS)

The Human Research Ethics Application reviewed by the HREC was:
Version: 1.03
Date: 21 May 2024

The approval is for a period of 5 years from the date of this e-mail **(21 May 2024)**

[redacted]

2023/ETH02415: Application HREA - Approved

[redacted]

Date of Decision Notification: **01 Nov 2023**

Dear [redacted]
Thank you for submitting the following Human Research Ethics Application (HREA) for HREC review;

2023/ETH02415: Recurrent valve frame infolding in the 34mm self-expanding Medtronic Evolut Pro+ transcatheter valve system, a single centre case series

This Application was reviewed as a **Low or negligible risk review pathway** and was initially considered by the **Northern Sydney Local Health District Human Research Ethics Committee** at its meeting held on **31 Oct 2023.** The project was determined to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was **APPROVED**.

This email constitutes ethical and scientific approval only.
This project cannot proceed at any site until separate research governance authorisation has been obtained from the Institution at which the research will take place.

This project has been Approved to be conducted at the following sites:

- **Royal North Shore Hospital**

The following documentation was reviewed and is included in this approval:

- Research Protocol, Version 1 dated 24 Oct 2023
- Case Report Consent form, Version 1.0 dated Oct 2023

Application Documents - (link will only be active for 14 days from the decision date. The approved documents are also available to download from forms section of this project in REGIS)

The Human Research Ethics Application reviewed by the HREC was:
Version: 1.00
Date: 24 Oct 2023

The approval is for a period of 5 years from the date of this e-mail **(01 Nov 2023)**

Participant Information Sheet/Consent Form
Interventional Study - *Adult providing own consent*

Royal North Shore Hospital/North Shore Private Hospital

Title	Prospective observational study on the accuracy of predictors of high-grade atrioventricular CONDUCTion block after Transcatheter Aortic Valve Implantation
Short Title	CONDUCT TAVI
Protocol Number	Version 0.6
Project Sponsor	Investigator Initiated Study - Supported by Northern Sydney Local Health District
Coordinating Principal Investigator/ Principal Investigator	Professor Ravinay Bhindi
Associate Investigator(s)	Dr Karan Rao Dr Peter Hansen Dr David Whalley Dr Usaid Allahwala Mitchell Cowan Natasha Saad Dr Kunwardeep Bhatia Dr Bernard Chan Dr Hari Sritharan
Location	Royal North Shore Hospital / North Shore Private Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, CONDUCT TAVI. This is because you will undergo a transcatheter aortic valve implantation (TAVI) for your aortic valve. From prior experience and research, we know that a significant proportion of people who undergo TAVI will develop abnormal heart rhythms (particularly conduction problems) after their procedure. The aim of this research project is to develop more accurate ways of identifying people who are at risk of developing these abnormal heart rhythms after TAVI.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The purpose of this research is to develop better methods of detecting and predicting conduction problems following TAVI. This research involves the insertion of the BIOTRONIK BIOMONITOR III loop recorder, an implantable heart monitor to detect abnormal heart rhythms. This monitor has been approved for use in Australia. BIOTRONIK will be providing BIOMONITOR III loop recorders (the device for monitoring for rhythm problems) at no cost.

The results of this research will be used by Dr Karan Rao to obtain a PHD.
This research has been funded by the Northern Sydney Local Health District.

3 What does participation in this research involve?

Study procedures and assessments in this study will only be performed after this consent form has been signed. If you consent to participating in this study, you will initially be screened for eligibility. There are specific study criteria which may allow or preclude you from participating in this study. If you are eligible, the following study procedures and activities will occur starting from the days leading up to your TAVI and ending two years after your TAVI.

During the days leading up to your TAVI, an investigator will conduct an interview to collect information on your demographics, medical history and medication list. They will also assess and record your height, weight and vital signs. An electrocardiogram (ECG or heart tracing) will be performed at this visit, which is routine care.

During your TAVI procedure, we will rapidly pace your heart before and after the procedure and test the speed of conduction within your heart using a pacing wire. This pacing wire is inserted into your groin and positioned to the corner of your heart as part of routine care before the TAVI, in case you have any rhythm problems during the procedure.

Immediately after your procedure or prior to your discharge from hospital, we will insert the implantable heart monitor under the skin in your chest. It is approximately the size of a USB and is inserted using a minimally invasive technique. This will detect any abnormal heart rhythms and upload them to a secure BIOTRONIK online database. You will be provided with a home monitoring device that will upload this data while you sleep. The heart monitor battery allows for approximately three years of monitoring. After the battery is depleted, the monitor will stay in your body under your skin.

After you leave hospital, we will see you at our clinic after 28 days, 6 months, and 12 months s. At these visits, we will check how you are going, check your medications and perform another ECG (these heart tracings are part of routine care). At each visit, we will also perform a manual check of your implantable heart monitor (however, any abnormal rhythms that occur between visits will be flagged using an alert system to allow us to act on them more quickly).

The research will be monitored by a team of researchers and doctors at Royal North Shore Hospital and North Shore Private Hospital who are experienced in Cardiology, Interventional Cardiology, Electrophysiology and Cardiac Research. This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

4 What do I have to do?

There are no specific instructions or actions that you will have to take before or during your TAVI. After the TAVI, we would like to see you at our clinic at 28 days, 6 months, and 12 months After your heart monitor has been implanted, we will monitor the results for you and contact you if action needs to be taken for an abnormal rhythm. There are no specific lifestyle, dietary or medication restrictions. You will still be able to donate blood.

5 Other relevant information about the research project

Approximately 205 people will be taking part in this project and we aim to monitor everyone in the same way. There will be two hospitals involved in this project - Royal North Shore Hospital and North Shore Private Hospital.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Royal North Shore Hospital or North Shore Private Hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. If you wish not to take part, you will receive the standard of care for TAVI. If you choose not to participate, we will not be pacing your heart during the TAVI, you will not receive an implantable heart monitor and you will not be required to follow-up in our clinic.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research. However, possible benefits include the recognition of abnormal heart rhythms by the implantable heart monitor. The monitor may allow us to detect abnormal and potentially dangerous heart rhythms before you notice them yourself. This could then allow us to treat these rhythm problems before they lead to more serious consequences such as fainting and death.

We also hope that this research project will be helping people who undergo TAVI in the future.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects. Note that this study excludes pregnant women.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

The risks associated with implantation of the heart monitor include minor bleeding (1%), pain (<1%), rash (<1%), problems with wound healing (<1%), problems with device positioning (<1%) and infection (<1%). The overall risk of a complication requiring invasive intervention or device removal is <1%. Should you experience any complications related to the implantation of your heart monitor, you will be reviewed by a study doctor and provided with the necessary treatment

The risks of heart pacing and heart conduction testing includes inducing an irregular heart rhythm called atrial fibrillation (<1%), which will be immediately detected by our monitoring. If this occurs, your rhythm will spontaneously return to normal in the majority of cases. However, if this does not occur, you would be treated with medications or an electric shock to aid in this process.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

11 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

It may also be necessary for you to take medication during or after the research project to address side effects or symptoms that you may have. You may need to pay for these medications and so it is important that you ask your doctor about this possibility.

12 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

13 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• Devices/monitoring being shown not to be effective
• Devices/monitoring being shown to work and not need further testing

14 What happens when the research project ends?

After the project ends (1 year after your TAVI), your implanted heart monitor will continue monitoring your heart rhythm for the remainder of its battery lifespan (around 3 years in total). During this time, any abnormal rhythms will be referred to your cardiologist who will contact you if necessary. After the project ends, you will not be contacted further about this research project.

Part 2 How is the research project being conducted?

15 What will happen to information about me?

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. It will not be used for clinical or other non-research purposes.

Any information obtained in connection with this research project that can identify you will remain confidential. Your information and data will be kept in a secure database only accessible by designated research investigators. The data will be re-identifiable (coded), which also means we will not be directly storing personal identifiers including your name, date of birth and address. Data will be retained for a minimum of 15 years post study completion or last publication. It will remain re-identifiable (coded) until it is destroyed. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Data from the implantable heart monitor is automatically uploaded and stored on a secure database hosted by BIOTRONIK. This data will be only accessible to designated research investigators and will be stored on the BIOTRONIK database as per routine care for BIOTRONIK heart monitors.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and NSW privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for the future research described in Section 16 that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

16 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital. There are no other guaranteed forms of compensation.

17 Who is organising and funding the research?

This research project is being conducted by Professor Ravinay Bhindi, the Director of Cardiology at Royal North Shore Hospital and North Shore Private Hospital.

BIOTRONIK will be providing BIOMONITOR III implantable loop recorders (heart monitors) at no cost.

BIOTRONIK may indirectly benefit financially from this research project if, for example, the project's outcomes favour the use of loop recorders after TAVI in the future

You will not benefit financially from your involvement in this research project. In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

There are no further declarations or conflicts of interest.

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Northern Sydney Local Health District.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Approval has been given by Royal North Shore Hospital (Northern Sydney Local Health District) and North Shore Private Hospital (Ramsay Health).

19 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 02 9439 5290 or any of the following people:

Clinical contact person

Name	Professor Ravinay Bhindi
Position	Principal Investigator
Telephone	02 9439 5290
Email	ravinay.bhindi@sydney.edu.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Research Office
Position	Research Governance Officer
Telephone	02 9926 4590
Email	NSLHD-Research@health.nsw.gov.au
Reference	2021/STE02507

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Northern Sydney Local Health District
HREC Executive Officer	Executive Officer
Telephone	02 9926 4590
Email	NSLHD-Research@health.nsw.gov.au

Consent Form - *Adult providing own consent*

Title	Prospective observational study on the accuracy of predictors of high-grade atrioventricular CONDUCTion block after Transcatheter Aortic Valve Implantation
Short Title	CONDUCT TAVI
Protocol Number	Version 0.6
Project Sponsor	Investigator Initiated Study - Supported by Northern Sydney Local Health District
Coordinating Principal Investigator/ Principal Investigator	Professor Ravinay Bhindi
Associate Investigator(s)	Dr Karan Rao Dr Peter Hansen Dr David Whalley Dr Usaid Allahwala Mitchell Cowan Natasha Saad Dr Kunwardeep Bhatia Dr Bernard Chan Dr Hari Sritharan
Location	Royal North Shore Hospital

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Royal North Shore Hospital / North Shore Private Hospital concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to
Participant's Signature (please print) _____

Signature Date

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	Prospective observational study on the accuracy of predictors of high-grade atrioventricular CONDUCTion block after Transcatheter Aortic Valve Implantation
Short Title	CONDUCT TAVI
Protocol Number	Version 0.6
Project Sponsor	Investigator Initiated Study - Supported by Northern Sydney Local Health District
Coordinating Principal Investigator/ Principal Investigator	Professor Ravinay Bhindi
Associate Investigator(s)	Dr Karan Rao Dr Peter Hansen Dr David Whalley Dr Usaid Allahwala Mitchell Cowan Natasha Saad Dr Kunwardeep Bhatia Dr Bernard Chan Dr Hari Sritharan
Location	Royal North Shore Hospital

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Royal North Shore Hospital / North Shore Private Hospital.

Name of Participant (please print) _____

Signature _____ Date _____

(If participant unable to sign declaration above, please detail the circumstances in this box):

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project. Note: All parties signing the consent section must date their own signature.

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