CLINICAL OUTCOMES ASSOCIATED WITH CARDIAC IMPLANTABLE ELECTRONIC DEVICES

By

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To my dearest parents Dr. Muhammad Munawar

and Mrs. Futikah Munawar,

my beloved husband Henry Michael Pattie,

and my children Nayla and Rifqy

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Abstract

The use of cardiac implantable electronic devices (CIEDs) has been increased dramatically in term of numbers as the broadening indications, not only for bradycardia management, but also for treating ventricular arrhythmias and preventing sudden cardiac death. Despite the undeniable benefit of CIED impact in patients with symptomatic conduction disease in prolonging life and improving quality of life, there are some deleterious effects related to long-term exposure to CIED. This thesis evaluates the comprehensive outcomes associated with CIED implantations.

In this thesis, literatures were reviewed to allow comprehensive discernment of factors affecting short-term and long-term clinical outcomes of the CIEDs, including the understanding of basic electrochemistry of the CIED generator, factors related to acute complication during CIED implantation procedure, clinical outcomes after implants, and effect of magnetic resonance imaging in CIED.

In chapter 2, a comprehensive review of internal and external factors affecting device longevity was performed. The findings demonstrated significant variability in the provided longevity by all manufacturers as no standardised calculation to report the longevity. In this study, standardised numbers of longevity between manufacturers are provided to assist clinician with their clinical decision.

In chapter 3, information of prevalence of the short-term complication following CIED implants is provided. This study shows a low rate of complication related to the procedure.

Observation from this study have identified that longer procedure time is an independent predictor of complication after CIED implantation procedure.

Next three chapters concern the long-term outcomes related to CIEDs. Chapter 4 demonstrates the insight of PH as an unrecognised long-term risk following CIED implants. This study also identified the cardiac structural predictors, with left atrial size and mitral regurgitation as the independent predictors of PH development in CIED population. Chapter 5 provide the evaluation of CIED algorithms, including minimised ventricular pacing (MinVP), atrial preventative pacing (APP), and atrial antitachycardia pacing (aATP), to reduce the risk of deleterious effects related to CIED implantation. These studies failed to show any significant benefit in the utilization of MVP, APP, and aATP algorithm in general CIED with paroxysmal AF population. Nevertheless, our pilot study shown in chapter 6 demonstrated that in the subset of post AF ablation patients, there was a significant reduction in the AT/AF events.

In chapter 7, a comprehensive systematic review of the literature and a meta-analysis were conducted to define the safety of magnetic resonance imaging (MRI) in patients with CIEDs, especially non-MRI conditional devices. This study indicates that the use of MRI in non-MRI conditional is safe, inasmuch as a strict selection and monitoring protocol is utilized.

Statement of Original Authorship

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Publications and Communications to Learned Societies

Chapter 1 – Literature review

Chapter 2 – Predicted Longevity of Contemporary Cardiac Implantable Electronic Devices: A Call for Industry-wide "Standardized" Reporting

Manuscript:

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Presentation:

- Presented as poster:

  Comparative Analysis of Predicted Longevities of Cardiac Implantable Electronic Devices: Implications for Clinical Practice (Poster, 9th Asia Pacific Heart Rhythm Society 2016, Seoul, Korea)

Chapter 3 – Complications related to Cardiac Implantable Electronic Device Implants: A Multivariate Survival Analysis of 3,832 Patients

Manuscript:

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Chapter 4 – Transvenous Cardiac Implantable Devices and Pulmonary Hypertension: An Echocardiographic Evaluation in a Cohort Study

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- Presented as poster:

  Risk Factors of Pulmonary Hypertension Development in Patients with Permanent Pacemaker (Poster, 12th Asia Pacific Heart Rhythm Society 2018, Taipei, Taiwan)

Chapter 5 – Implication of Ventricular Pacing Burden and Atrial Pacing Therapies on the Progression of Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Presentation:

- Presented as Poster

  Implication of Cumulative Ventricular Pacing and Atrial Preventative Pacing on the Progression of Atrial Fibrillation: A systematic review and Meta-analysis (8th Asia Pacific Heart Rhythm Society 2015, Melbourne, Australia)

- Presented as poster

  Effectiveness of Cumulative Ventricular Pacing and Atrial Preventative Pacing on the Reduction of Atrial Fibrillation: A Systematic Review and Meta-analysis of Randomized Clinical Trials (Poster, 37th Heart Rhythm Annnual Scientific Session 2016, San Fransisco, USA)

Chapter 6 – Clinical Effectiveness of Atrial Pacing Therapies in Sinus Node Disease after Atrial Fibrillation Ablation (CEASE-AF): A Pilot Study

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- Presented as featured poster:

  Influence of Cycle Length Variation and Therapy Modes on Atrial Antitachycardia Pacing Therapy Efficacy among Atrial Fibrillation Patients with Dual Chamber Pacemaker (Featured Poster, 38th Heart Rhythm Annual Scientific Session 2017, Chicago, USA)

- Presented as oral presentation:

  Atrial Antitachycardia Pacing Therapy Efficacy Among Atrial Fibrillation Patients with Dual Chamber Pacemaker: Role of Atrial Cycle Length In Tachycardia Termination (Oral Presentation, 10th Asia Pacific Heart Rhythm Society 2017, Yokohama, Japan)

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Manuscript:

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Published.

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Invited Faculty Invitations

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Other Peer-reviewed Publications during Candidature

1. Wong GR, Lau DH, Middeldorp ME, Harrington JA, Stolcman S, Wilson L, Twomey DJ, Kumar S, **Munawar DA**, Khokhar KB, Mahajan R, Sanders P. Feasibility and safety of Reveal LINQ insertion in a sterile procedure room versus electrophysiology laboratory. Int J Cardiol. 2016 Nov 15;223:13-17. doi: 10.1016/j.ijcard.2016.08.113.

2. Middeldorp ME, Mahajan R, Elliott AD, Pathak RK, Twomey DJ, Wilson L, Stolcman S, **Munawar DA**, Kumar S, Lau DH, Sanders P. Premature Trigger of ERI in Medtronic EnRhythm Devices. Pacing Clin Electrophysiol. 2017 Jun;40(6):624-628. doi: 10.1111/pace.13073

3. Mahajan R, Perera T, Elliott AD, Twomey DJ, Kumar S, **Munawar DA**, Khokhar KB, Thiyagarajah A, Middeldorp ME, Nalliah CJ, Hendriks JML, Kalman JM, Lau DH, Sanders P. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. Eur Heart J. 2018 Apr 21;39(16):1407-1415. doi: 10.1093/eurheartj/ehx731.

4. Sanders P, **Munawar DA**, Pathak RK. Periablation Anticoagulation: Translating Research Into Clinical Practice. JACC Clin Electrophysiol. 2018 May;4(5):589-591. doi: 10.1016/j.jacep.2018.01.011.

5. Clarnette JA, Brooks AG, Mahajan R, Elliott AD, Twomey DJ, Pathak RK, Kumar S, **Munawar DA**, Young GD, Kalman JM, Lau DH, Sanders P. Outcomes of persistent and long-standing persistent atrial fibrillation ablation: a systematic review and meta-

analysis, 2018. EP Europace. 2018 Nov 1;20(FI_3):f366-f376. doi: 10.1093/europace/eux297.

6. Thiyagarajah A, Kadhim K, Lau DH, Emami M, Linz D, Khokhar K, **Munawar DA**, Mishima R, Malik V, O'Shea C, Mahajan R, Sanders P. Feasibility, Safety, and Efficacy of Posterior Wall Isolation During Atrial Fibrillation Ablation: A Systematic Review and Meta-Analysis. Circ Arrhythm Electrophysiol. 2019 Aug;12(8):e007005. doi: 10.1161/CIRCEP.118.007005.

Abbreviations

aATP	Atrial antitachycardia pacing
APP	Atrial preventive pacing
ARS	Atrial rate stabilisation
AF	Atrial fibrillation
AFl	Atrial flutter
AT	Atrial tachycardia
AC	Auto capture
AVSH	AV search hysteresis
BOL	Beginning of life
CIEDs	Cardiac implantable electronic devices
CRT-D	Cardiac resynchronization therapy-defibrillator
CS	Coronary sinus
DVT	Deep vein thrombosis
DFT	Defibrillation threshold
EF	Ejection fraction
ERI	Elective replacement indicator
HRs	Hazard ratios
IRAF	Immediate after termination of AF
ICD	Implantable cardioverter defibrillator
IVC	Inferior vena cava
IQR	Interquartile range
ICE	Intra cardiac echocardiography

IRSplus	Intrinsic Rhythm Support
LVESV	Left ventricular end systolic volume
LVEDD	Left ventricular end diastolic
LV	Left ventricular
LRO	Lower rate overdrive
MRI	Magnetic resonance imaging
MVP	Managed ventricular pacing
MinVP	Minimizing ventricular pacing
OSA	Obstructive sleep apnea
PAV	Paced AV
PICM	Pacing induced cardiomyopathy
PPM	Permanent pacemaker
PMOP	Post Mode-Switch Overdrive Pacing
PEPS	Post-extrasystolic pause suppression
PAC	Premature atrial complexes
PHA	Proportional hazard assumption
PVI	Pulmonary vein isolation
PE	Pulmonary embolism
RAA	Right atrial appendage
RFA	Radiofrequency ablation
RCTs	Randomized controlled trials
RRT	Recommended replacement time
RV	Right ventricle -
RA	Right atrium
SAV	Sensed AV

SND	Sinus node dysfunction
SVC	Superior vena cava
SPAP	Systolic pulmonary artery pressure
TRV	Tricuspid regurgitation velocity
URO	Upper rate overdrive
VIP	Ventricular intrinsic preference

CHAPTER 1

Literature Review

1.1.Cardiac Implantable Electronic Devices: Backgrounds

The number of cardiac implantable electronic devices (CIEDs) implants, including permanent pacemaker (PPM), implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy-defibrillator (CRT-D), has risen significantly over the last two decades.[1,2] An increase in life expectancy causes demographic change with an aging population that subsequently increase the needs of CIED implants. This can also be attributed to a significant rise in risk factors of atrial fibrillation (AF) that is associated with sinus node disease (SND). In addition, the broadening indications for treating ventricular arrhythmias and preventing sudden cardiac death, and the arrival of the cardiac resynchronization therapy devices have also led to an increase in the use of CIED.[3] In Australia, the rate of PPM implantation increased from 565 in 2009 to 652 per 1,000,000 persons in 2013, a notable increase from around 200 per 1,000,000 persons in 1993.[4] there was an increase of the number of new ICD procedures from 37.0 per 1,000,000 persons in 2000 to 145.6 in 2009,[5] and continue to increase to 167 per 1,000,000 persons in 2013.[4] In USA between 1993 and 2009, it is reported that the use of PPM has increase by 55.6% from 121,300 in 1993 to 188,700 procedures in 2009, an increase from 47.6 to 61.6 cases in 100,000 person.[6] For ICD procedures, it has increased from 4.1 in 1993 to 46.2 cases per 100,000 persons in 2006.[1] In Western Europe, the PPM implantation rate increased from 82.9 to 93.8 cases per 100,000 persons, and the CRT devices implantation rate increased from 6.0 to 14.0 cases per 100,000 persons between 2005 and 2011.[7] In South Korea, although the number is much lower than USA and Western European countries, there was a significant increase of PPM cases during this period from 5.1 cases in 2009 to 9.3 cases per 100,000 in 2016. Similarly, ICD and CRT implant also demonstrated an increase from 0.6 to 1.9 per 100,000 persons, and 0.1 to 0.5 cases per 100,000 persons, respectively.[8] In Japan, CIED implantation rate is higher, with PPM implantation rate increased from 21.0 in 2001 to 27.2 cases per 100,000 persons in 2009, while the ICD implantation rate increased from 0.9 in 2001

to 4.2 cases per 100,000 persons in 2009.[2,9] Although the upfront cost associated with CIEDs implants is high, the cost-effectiveness of ICD and CRT-D devices is well established.[10,11] One of the major factors on the delivery of CIEDs worldwide is reimbursement system. Encouragingly, most countries are recognizing the role of pacing as a standard, public reimbursable therapy. However, there is yet limited public reimbursement for more advance devices such as ICD and CRT worldwide. The lack of knowledge, facilities and personnel are other important issues for optimal delivery of arrhythmia management.[12]

1.2.Historical Milestones in the Development of Cardiac Implantable Electronic Devices

Invention of CIEDs has been a major breakthrough in the field of modern medicine. The first implantation of a transvenous electrode into the right ventricle with external pacing device was successfully inserted in August 1958 by Furman in New York, USA, and succeeded in stimulating the heart for 96 days.[13] Later in this momentous year, the first human pacemaker device aiming to provide bradycardia support was implanted by Senning, the surgeon, and Elmqvist, the technologist, using epicardial leads and a rechargeable battery.[14] By the mid 1960s, cardiologists were making attempts to insert transvenous leads into the right ventricle. It was started with an insertion of temporary pacing wire via the basilic vein by a right cubital fossa cut-down and guided to the right ventricle under fluoroscopic control for four to five days until the patient's cardiac conduction recovered. Following this, a permanent transvenous endocardial pacing system became more common.[15] These pioneers laid the foundations of electrical therapy for the heart.

The initial development of CIED is a decade of asynchronous pacing, with the goal of treatment is to prevent asystole in cardiac arrest and Morgagni-Adams-Stokes syndrome. Permanent pacing of these patients in this era were fixed rate units, however, it substantially changed the

prognosis from very poor to the one in normal population of similar age. Notwithstanding, greater improvement of quality of life results from CIED, it was tempered by the fragility of the pacing systems that affecting the reliability of the devices.

In the 1970s, the innovation of the “demand pacemaker” is attributed to Berkovits. In this device, if a spontaneous cardiac signal is detected, it resets the timing for a complete timing cycle, thus competitive stimulus with vulnerable phase of intrinsic ventricular conduction will be avoided. This will reduce the risk of inducing ventricular tachyarrhythmias. Later in this decade, the DDD pacemaker was also introduced by Funcke, a combination of the atrioventricular synchronous pacing to maintain a more physiological conduction.[16]

In the earlier era of transvenous pacing system, leads were unipolar with high polarization electrodes, low electrode-tissue impedance, excessive current drain, no fixation mechanism, and no lumen in which to place a stylet for lead positioning. The lead implantation procedures were usually long and the irradiation to both patient and operator excessive (figure 1). There were very common complications related to the procedure, such as lead dislodgement, and exit block.[15]

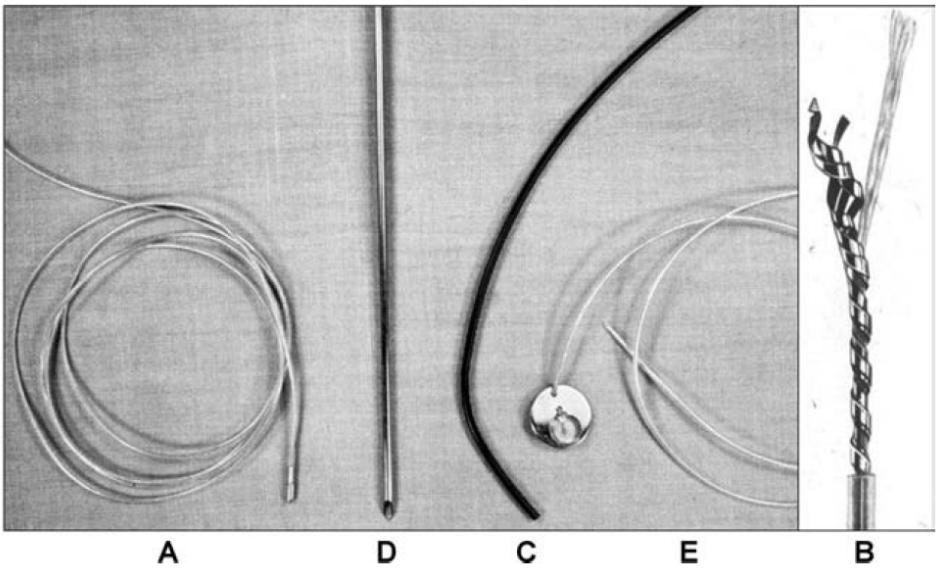


Figure 1. *The Elema-Schonander EM 588 lead and the hardware required for implantation (circa mid 1960s to early 1970s). (A) The lead came in lengths of about 130 cm and had no connector. The electrode size ranged from about 25 to 100 mm and there was no fixation device. (B) There was a Terylene core, stainless steel ribbon conductor, and polyethylene insulation. (C) The lead was inserted retrograde into a Cournand catheter as the electrode tip was larger than the catheter lumen. (D) A large bore needle was used to pass the lead through the subcutaneous tissues from the subclavicular to the suprapubic region. (E) Because the lead was unipolar, an indifferent plate inserted subcutaneously in the upper thigh was required to externally pace the heart.(Reproduced with permission from Mond et al, 2008)*[15]

The development of the implantable cardioverter-defibrillator was also a revolutionary step in the history of medicine. The first generation of ICD system involved epicardial patches placed through thoracotomy. The pulse generators were large and required placement in an abdominal pocket, with shock energy delivered through a free-floating endovascular titanium spring coil as the anode and the patch as the cathode. These first-generation ICD systems had a high risk of complications, particularly in the large endovascular coil, including superior vena cava thrombosis, coil fracture, insulation failure, and coil retraction into the subclavian vein caused by lack of a lead anchoring sleeve.[17] The second-generation ICD devices were fully epicardial systems, with shock delivery between two epicardial patches and tachyarrhythmia sensing through an epicardial lead. These systems lead to ongoing infection and pericarditis risk, and a perioperative mortality around 4%.[18] Not until early 1990s, advances in pulse generator design and technology resulted in miniaturization for infraclavicular pectoral implantation, allowing

entirely endocardial defibrillation, sensing, pacing lead system. However, the earlier version of the lead was large and bulky, predisposing to venous occlusion and subclavian crush,[19] lead failure was frequent, demonstrating a progressive late incidence related to both conductor fracture and insulation defects.[20]

1.3.Engineering of Current Cardiac Implantable Electronic Devices

1.3.1. Generators

Cardiac implantable electronic devices system consists of a pulse generator or can, which contains the battery and capacitors. The battery converts chemical energy into electrical energy, depending on the type and amount of the materials participating in the electrochemical reaction within the battery. The first generation of pulse generators were powered by zinc-mercury cells, which were large, unreliable, and prone to sudden output failure that potentially lead to premature power source failure (figure 2).[15]

The next generation of battery is lithium/iodine (Li/I_2), that has become the power source of choice for cardiac pacemaker since firstly implanted in 1972. Since then, improvements in cell chemistry, cell design, and modeling of cell performance have been made lead to favour the use of this battery system. When the current demand is low, it is difficult to improve on the performance of Li/I_2 batteries; their high energy density and low rate of self-discharge result in good longevity and small size.[21] Lithium/carbon monofluoride (Li/CFx) batteries were introduced in commercial coin-type batteries in 1976. The energy density of this battery is similar to that of the Li/I2 battery; however, the battery can deliver currents in the milliampere range without significant voltage drop. Silver vanadium oxide (SVO) plus CFx has been developed as the cathode of the new lithium battery chemistry since 1999. SVO has high power capability and is the same cathode material used to power ICDs. The blend of the SVO and

CFx materials as cathodes of a battery results in a primary battery that has an energy density equal to that of a lithium/iodine battery with approximately 100 times more power capability.[21,22]

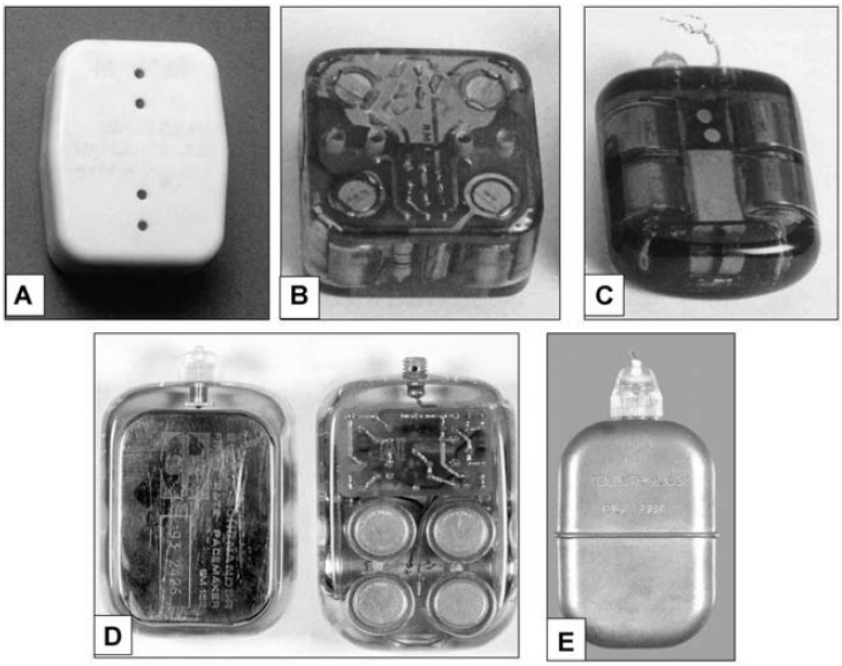


Figure 2. *Five early model unipolar implantable pulse generators used at the Royal Melbourne Hospital. (A) Devices, UK: The lead, which was attached to the pulse generator has been cut off. To prevent fluid ingress, the pulse generator is encased in silicone rubber (circa 1963). (B) Royal Melbourne Hospital-built pulse generator: There are four zinc-mercury cells bonded to a circuit board and encased in epoxy resin (circa 1965). (C) Elema-Schonander, Sweden (circa ~1968). (D) Elema-Schonander, Sweden: Two views are shown. On the left is the smaller VOO model with five zinc-mercury batteries obscured by the indifferent plate (anode). The VVT model on the right is larger because of more electronics and space for only four zinc-mercury cells (circa 1970). (E) Telectronics, Australia: The VVT model shown was the first pulse generator to be encased in titanium and thus hermetically sealed. The electronics were on a microcircuit. There was fear that the pulse generator would explode because of hydrogen gas build-up in the zinc-mercury cells, which could not be vented. The cold welding technique designed by Telectronics created an elevated central waist which could erode the insulation of leads lying under it (circa 1971). (Reproduced with permission from Mond et al, 2008)*[15]

In ICDs, generators have decreased significantly in size because of significant advancements in battery and microprocessor technologies, and most of the generator volume is occupied by its battery and capacitor. There are three different types of battery chemistries, which are lithium/silver vanadium oxide, lithium/manganese dioxide, and lithium/layered SVO-CFx. These battery types affect the shapes of the discharge curves, resistance of the battery, and effects of time since implant. Most of the time the ICD battery are used in much the same way

to pacing battery, which delivers a low current drain as required for sensing and pacing and has negligible effect on the battery voltage.[21] Whilst low current drain is determined by the batteries chemical energy, high-voltage defibrillation needs capacitors as a passive device that store the energy before allowing the device to deliver a therapeutic, high-voltage, high-energy shock through the lead system to the heart. When it is necessary to charge the high-voltage capacitors, either for capacitor formation or to deliver a therapeutic shock, the voltage drops quickly by about 1 V, then, after the capacitors are charged, recovers quickly to near the previous value.[21]

Advances in battery chemistry and component design led to an advance innovation of pacemakers without the need for pacing leads. A state-of-the-art technology, leadless pacemaker, is a self-contained right ventricular single-chamber pacemaker providing pacing, sensing, and rate-response delivery. Two leadless pacing systems are currently clinically available: (1) the Nanostim Leadless Cardiac Pacemaker (LCP; St. Jude Medical), and (2) the Micra Transcatheter Pacing System (TPS; Medtronic).[23] Both systems are completely intracardiac, and in both cases, the generator and the pacing and sensing electrodes are incorporated in a single capsule-shaped compartment implanted directly in the right ventricular wall.[24] The battery is lithium carbon monofluoride or lithium polycarbon fluoride and offers a higher energy density.[25] The cathode, in both systems, is located on the distal end of the pacemaker and is steroid eluting to reduce inflammation. For the Micra-TPS, the anode consists of a titanium ring in the proximal part of the pacemaker case, whereas for the Nanostim-LCP, most of the surface of the device serves as the anode.[24] Battery longevity of both systems is considered comparable to that of conventional pacemakers. The battery life of the Nanostim-LCP programmed at the standard settings (e.g., 2.5 V/0.4 ms, 600 Ω, 60 beats per minute [bpm], and 100% pacing) is reported to be 9.8 years. However, the projected battery life at the alternative settings of 1.5 V/0.24 ms, 500 Ω, and 100% pacing increases to 14.7 years. The

battery life for the Micra-TPS is reported to be 4.7 and 9.6 years at the standard and alternative settings, respectively.[26]

1.3.2. Leads

Leads are important in pacing system to travel the signal from the can to contact the myocardium, to deliver a depolarizing pulse and to sense intrinsic cardiac activity. Pacing occurs when a potential difference (voltage) is applied between the 2 electrodes. With unipolar pacing, current is delivered between the lead tip and the pulse generator which may potentially be affected by myopotential and electromagnetic interference.[27,28] The development of bipolar pacing leads, which measure the potential difference occurs between the lead tip (cathode) and a proximal ring (anode), is very useful in minimizing electromagnetic interference and far-field oversensing,[29] however, this required a major revision of lead body design and structure, because two longitudinal conductors needed to coexist inside the lead, separated only by a thin layer of insulation. The development of passive (electrically inert tines anchor the lead) or active (with an electrically active helix at its tip for mechanical stability) lead could dramatically reduce the rate of lead dislodgement compared to the previous version of pacing leads.[30]

In the transvenous ICD leads, the basic elements in pacing leads such as conductors, insulation, electrodes, fixation mechanisms, and connector terminals are also found. In addition, however, ICD leads contain the high-voltage circuitry that links the pulse generator with one or two high-voltage shock coils located on the lead body, which is the defining feature of the ICD lead. Single coil models consist of one shock coil wrapped around the distal lead body, 5 to 6 cm in length and positioned in the right ventricle. Meanwhile, dual coil leads consist of the second shock coil located either 17 cm or 21 cm proximal to the shaft end of the RV coil, with this

superior vena cava (SVC) coil. Dual coil leads are correlated to a lower defibrillation threshold (DFT), with a 14% reduction and reduce the risk of higher DFT by three times compared to single coil.[31] The materials used in shock coil construction are generally platinum-iridium alloy or platinum alloy–clad tantalum. Titanium coils produce metallic oxides during high-voltage shocks that prevent their use in ICD leads. Some data suggest that iridium oxide coating may improve lead porosity and a meaningful reduction in DFT.[32]

Standard pacemaker lead designs incorporate a stylet lumen to allow lead placement using a stylet during implant or use of a locking stylet for lead extraction. A new approach aimed to decrease lead diameter involves eliminating the stylet lumen, which can reduce around 40% of the diameter of a standard 7-Fr pacemaker lead. The SelectSecure™ model 3830 lead (Medtronic Inc., Minneapolis, MN, USA) is a bipolar, fixed-screw, steroid-eluting, lumenless, 4.1-Fr pacing lead. Removal of lumen allows the use of cable-wound conductors for lead body tensile strength, extra electrical insulation for reliability, and extractability without the need for a locking stylet.[33] The reliability of cable conductor designs in ICD leads (e.g., Medtronic Model 6932 lead) has been established.[34] In a manner similar to catheter delivery of left heart leads, lumenless right heart leads can be delivered to any location in the right heart using either a fixed shape or a deflectable catheter.[33]

1.4.Longevity of Cardiac Implantable Electronic Devices Generators

Longevity of pacing devices is a crucial issue when considering device selection. There are two major factors affecting the projected longevity. They are: 1) non-modifiable factors, such as battery chemistry, housekeeping current, lead structures, and impedances; and 2) programmable factors, such as pacing burden, pacing output and pulse width, and device algorithms.

1.4.1. Non-modifiable factors

Projected longevity of the pacing device is determined by battery capacity and current drain of the energy used by the pacemaker.[35]

1.4.1.1.Battery chemistry

The trend of recently developed devices have been manufactured to be smaller and thinner generators yet with the goal of increased longevity. As has been shown in our study, all manufacturers use lithium-based chemistry for the battery to achieve this aim, which has high energy density, low intrinsic current depletion, and progressive end of life.[36] However, more sophisticated function equipped in modern pacing devices will increase the housekeeping current, which consequently inflicts inefficiency of energy utilization and decreases the longevity.

1.4.1.2.Housekeeping current

Up to 50% of the current drain from the battery is used for pacing, However, it is notable that not all the energy will be transferred from pacemaker to myocardium. Some amount of the energy, called housekeeping current, is used internally to keep the pacemaker functioning, sensing, and storing any events when pacing pulses are inhibited.[37,38]

1.4.1.3.Lead structures

The materials used for lead electrodes included titanium, anodized platinum, platinum-iridium alloys, Elgiloy (an alloy of cobalt, iron, chromium, molybdenum, nickel, and manganese), and vitreous carbon. In general, minor corrosion seen in Elgiloy and platinum alloys when in situ for extended periods, with most having reasonable in vivo performance and longevity,[39]

although vitreous carbon cathodes have particular strength, inertness, and long-term electrical reliability.[40]

The surface area of the lead electrodes seems more important than their material composition. A large cathodal surface area in contact with endocardium results in a low current density at the electrode-tissue interface and consequently a higher capture threshold. As the surface area of tip electrodes were reduced, better thresholds can be achieved and higher tissue-electrode impedances were also seen, and this increased pulse generator longevity.[30]

Performance of active- and passive-fixation leads is considered similar in general, with some differences related to their construction. Passive leads tend to have lower chronic thresholds with higher impedances that prolong pulse generator longevity,[41] however, active leads tend to be more stable and easier to extract.

1.4.1.4.Lead impedance

The relationship among voltage, current, and resistance is defined by Ohm's Law (V = IR), where V = voltage, I = current, and R = resistance. Pacing lead conductors are designed to have a low internal resistance, to minimize wastage of energy as resistive heat. Because permanent pacemakers generate a constant voltage, the higher the pacing resistance (the load, resistance of current passage through tissue) the lower the current drain (I = V/R), and the lower the rate of battery depletion per each pacing pulse.[42] Berger et al reported a study with 40 patients randomised to high versus normal impedance ventricular leads on pacemaker generator longevity. In this study, it is proven that the extrapolated generator longevity was significantly longer in the high impedance lead group, as compared to the standard impedance lead group.[43]

Thus, lead tip electrodes are optimized to have a relatively high resistance to minimize current flow and preserve battery.

1.4.2. Programmable factors

1.4.2.1.Pacing burden

It is widely recognized that the higher number of pacing pulses reflects the more energy delivered to the heart and accordingly, the longevity of the pacemaker will be decreased. The energy required to pace the myocardium depends on the programmed pulse width and on the voltage delivered between the electrodes. An exponential relationship (strength-duration curve) exists between the stimulation threshold and the pulse amplitude and duration. This is clinically relevant, in that optimizing the pulse width and amplitude can significantly affect current drain and battery longevity.[42] A recent published meta-analysis showed that substantial reduction in the longevity was noted when the device paces at 100% as compared to 50%. This is due to a linear increase of the current drain with increased pacing rates, which negatively affects the longevity.

1.4.2.2.Pacing output and pulse width

Pulse generators allow the clinician to program both the pacing output (in volts) and the pulse duration (in milliseconds (ms)). The stimulation threshold is a function of both these parameters. The exponential shape of the strength-duration curve must always be considered when programming the output pulse to ensure an adequate margin of safety between the delivered stimulus and the capture threshold.

The longevity of the generator is typically associated to a specified set of programmed parameters by the physicians. A common clinical concern for programming of the pulse

generator to optimize battery longevity relates to whether it is more useful to program the amplitude or the duration of the output pulse. Based on examination of the strength-duration relationship, it seems that reducing voltage of the pulse is more efficient, because the current drain varies as the square of voltage. This would mean a higher increase in pulse width can yield a similar current drain than an output increase, but the safety factor would be significantly better in the setting of a patients with high threshold.[44]

1.4.2.3.Device algorithms

Pacemaker programming and algorithms equipped within a device that have an impact on the pacing rates play an important role in the longevity. Some manufactures provide algorithms to reduce unnecessary ventricular pacing, to suppress atrial fibrillation (AF) and reduce the development of pacing induced cardiomyopathy. These algorithms include AV Search Hysteresis (AVSH) that periodically lengthen AV delay, and managed ventricular pacing (MVP) that combine the advantage of AAI pacing with the safety of DDD pacing, to allow intrinsic ventricular conduction.[45-47] Previous studies showed that as compared to DDD mode, activation of AVSH was associated with significant longevity increase of 9 months, while MVP could escalate the mean of longevity by 23 months.[48,49] Likewise, the algorithm designed to reduce atrial pacing such as Sleep and Sinus Preference (SP) showed a similar result. This algorithm sets the sleep function with a different lower rate during a programmable time period. Enabled SP algorithm was found to be associated with 3 months projected longevity improvement.[49] On the other hand, atrial preventive algorithm (APP) that is aimed to suppress atrial arrhythmia uses the principle of pacing faster than intrinsic atrial rate, which typically results in more than 90% of atrial pacing percentage. Nevertheless, to the best of our knowledge, its effect on the real longevity has not been studied yet. One other factor that is also important in the longevity includes minimizing the pacing voltage with the features such as AutoCapture

(AC), which is able to verify ventricular capture on a beat-to-beat basis, and automatically adjust output closely to pacing threshold. This algorithm has been shown to increase the longevity by 16%, and reduce the expected pacing-related cost up to 42% over a 10-year follow up.[50,51]

1.5.Cardiac Implantable Electronic Device Insertion Procedure

In general, CIED implantation procedure are considered safe. This procedure involves placing a pulse generator in a pre-pectoral pocket inferior to the clavicle on the non-dominant side where possible. There are three different option for incision based on the approach of venous access, which are dectopectoral, horizontal, and oblique incision. Venous access can be gained through the axillary[52] or subclavian vein with Seldinger technique. Most operators puncture blindly using the incisura of manubrium sternum as the anatomical landmark for subclavian vein puncture. Nevertheless, venogram or ultrasound guided puncture can be used to show the vein.[53] Another option to gain venous access is via cutdown to the cephalic vein. Successful cephalic vein approach highly depends on learning curve; however, the cephalic vein can be isolated easily in most patients. The vein runs along the deltopectoral groove, with the anatomical landmark of the fatty pad located at the deltopectoral groove. Once the fatty pad is seen, the cephalic vein lies underneath it, and can be easily isolated.[54]

In dual chamber system, a ventricular lead is most placed in the right ventricular (RV) outflow track, septum or apex, and a second lead can be placed into the right atrium (RA) as required. No difference in the technique of implantation between PPM and ICD leads. Following satisfactory parameter checks, the leads are fixed into position, using a screw helix which is deployed into the myocardium in an active lead system or a barbed tip to passively tether the trabeculated myocardium in a passive lead system. Within 4–6 weeks following implantation,

fibrosis of the tip normally occurs, which permits more durable lead fixation. Different to RA and RV leads, the technique of left ventricular (LV) leads insertion is more challenging. The transvenous approach via the coronary sinus (CS) was first published by Daubert in 1998 and has become the implantation technique of choice.[55] The target vein of the LV lead placement is one of three veins, which is anterolateral, lateral, or posterolateral vein. The LV lead tip should be placed as far as possible from the tip of the RV apex lead. The best view for this purpose is from the LAO position.

1.6.Short-term Complications associated with CIED implantation

As indications for CIED have increased, the number of CIED implant is increasing over the years, however, complications can occur and can be very morbid, because patients with more comorbidities often requiring long and complex procedures. The majority of studies report an overall risk of any complication occurring at 5–6%.[56,57] Short-term complications include haemo/pneumothorax, bleeding and haematoma, infection, lead displacement and cardiac tamponade.

1.6.1. Pneumothorax

The occurrence of pneumothorax is reportedly < 2%, with an attendant increase in morbidity, mortality, prolonged hospital stays and cost of care, especially when a chest tube is required.[58,59] Puncture of the axillary vein over the first rib is one such technique to reduce this risk. A recent non-randomized study enrolling 1,264 patients found an incidence of pneumothorax at 0% when puncturing axillary vein over the first rib vs 2.4% when using the conventional proximal subclavian access (p=0.0006).[60] The use of ultrasound to guide access is proven to minimise the risk of pneumothorax.[61,62]

1.6.2. Lead dislodgement

Lead dislodgement is a well-recognized complication during implantation of CIED. Previous reports demonstrated that the incidence of lead dislodgment varied between 1-3.3%,[63-66] with the majority of the LD events occurred in the first 24 hours after the procedure.[67] Ghani et al showed that the right atrial (RA) lead (1.9 %) showed the most frequent lead dislodgement compared with the right ventricular (RV) pacemaker lead (0.3 %) or ICD lead (1.8%). Only 1-2.1 % coronary sinus (CS) leads dislocated requiring reintervention.[64,66]

1.6.3. Lead failure

Lead failure in ICD occurs more frequent than pacing lead failure. It is shown that the ICD lead (0.8 %) showed the most frequent lead malfunction compared with the RA lead (0.1 %).[64] Complication of lead failure, especially in ICD, can lead to sudden death. This can occur not only by loss of pacing support in pacemaker-dependent patients, but also by causing recurrent inappropriate shocks due to oversensing of lead noise as most often seen. Ventricular fibrillation can be induced by these shocks, which the system may then not be able to defibrillate successfully.[68]

Kleemann et al revealed that the incidence of lead fractures in ICD implanted between 1992 and 2005 was only 60% at 8 years, mainly from insulation defects, including in silicone-based leads. One in five leads implanted for a decade or longer failed.[69] The majority of RA and RV lead malfunction occurred after the 2nd month following implantation.[64]

1.6.4. Bleeding/hematoma and cardiac tamponade

Defibrillator implantation carries a higher risk of haematoma and tamponade given the heavier

construction of the lead and pulse generator. All lead/screw perforations were subacute and the incidence was very low (0.6–5.2 %).[66,70-72]

1.6.5. Infection

As a result of increasing incidence and complexity of CIED treatment, infection is one of the most common complication associated with CIED procedures. CIED infections increased mortality and morbidity and imposed a substantial financial burden resulting from prolonged hospital stays, long duration of antibiotic therapy, management of sepsis and complications, device extraction and reimplantation.[1] The rate of CIED infection has been estimated at 0.5 % with primary implants and 1–7 % with secondary interventions.[1,73,74] Some data have shown a tendency of increased rate of CIED infection, especially in the first few months after installation.

1.7.Long-term Predicament in Cardiac Implantable Electronic Devices

1.7.1. Thromboembolic events related to transvenous CIED

Despite their effectiveness in treating cardiac arrhythmias, a transvenous device system represents a foreign body in contact with the bloodstream and potentially form thrombus.[75] A study in the patients undergoing periablation echocardiogram (either transthoracic, transesophageal, or intra cardiac (ICE)) showed that the incidence of lead thrombus in patients with CIED was around 1.4%.[76] Another study using ICE only as the modality to investigate lead-thrombi in CIED in patients undergoing ablation demonstrated a higher incidence at 30% of the patients,[77] and are seen more frequently in right atrium (RA) than in the right ventricle (RV).[78] According to Virchow's triad, pathogenesis of thrombus depends on three factors endothelial damage, stasis of blood and hypercoagulable states. Transvenous leads can cause both endothelial damage and stasis of blood.[79] Lead-related thrombi are adherent to the foreign

body and rarely floated in the RA. The thrombus can dislodge to the pulmonary circulation and result in subclinical pulmonary embolism (PE) in up to 48% of cases with transvenous CIED leads.[80,81] A published study from autopsy also confirmed the evidence of right atrial PPM lead thrombosis in 14% of the patients at 4 years after implantation.[78] Intersentingly, many studies also demonstrated that the patients did not present with a history of clinically recognized pulmonary embolism and remained aymptomatic.[75,77] Therefore, the clinical implications of these thrombi are unclear.

Therapeutic options to avoid the thromboembolic events include the use of anticoagulation, thrombolytic therapy and surgical embolectomy.[82] Unfortunately, previous report showed that anticoagulation failed to reduce thrombus size and thrombolytic therapy has been shown to potentially result in thrombus fragmentation and pulmonary embolization.[83]

1.7.2. Pacing induced cardiomyopathy (PICM)

The risk of left ventricular (LV) cardiomyopathy induced by RV pacing, known as pacing induced cardiomyopathy (PICM), has been well described over the years,[84,85] with an incidence up to 26% in patients with RV apical pacing over 7 years of follow up.[86,87] The risk of PICM persists even after years of PPM exposure as it can be developed as early as one month and as late as nine years following pacemaker implant.[88]

The adverse haemodynamics associated with normal pacing system was firstly recognized in the 1980s, with the relative indications for permanent pacing including individuals whose primary indication for pacing was sinus node dysfunction or pacing in intermittent basis.[89] This hemodynamic deterioration (known as “pacemaker syndrome”)[90] was usually associated with a loss of atrioventricular synchrony, mitral regurgitation, inter-/intraventricular asynchrony,

arrhythmia induction, and neuroendocrice reflexes. A strong negative atrial kick that caused by atrial contraction against closed atrial valves, especially if retrograde conduction with VA interval more than 100 ms, will reduce cardiac output and lead to pacemaker syndrome due to reflexes causing a fall in peripheral vascular resistance. [91]

Another study suggested that in even in AV synchronous ventricular pacing as in DDD, ischemia myocardium can occur that may result in triggering AF. Lee et al conducted a study in 24 dogs that divided into the group with AV-block due to AV junction ablation, undergoing long-term ventricular pacing and control group. The study groups were divided into the group programmed to VVI only and DDD pacing. This study showed that pacing from the right ventricular apex without AV synchrony (VVI group) was associated with heterogeneity of myocardial perfusion compared with that of the control group. Intermediate degrees of perfusion were also noted in the dual-chamber paced group. Cardiac tissue norepinephnin levels were higher in both DDD and VVI groups, compared with the levels in the control group. Both reduction coronary blood flow proven by thallium scan and an increase in tissue norepinephrine lead to ischemia that can result in further cardiomyopathy.[92]

Electrical remodelling after electrical pacing that result in cardiac memory (CM) was firstly described by Rosenbaum et al.[93] It is characterized by a changed T wave following 15 minutes to several hours of right ventricular pacing due to a change in heterogeneity of repolarization. This persistent change in the electrophysiological properties of the heart in response to a change in the sequence of electrical activation in the absence of significant structural changes is referred to as “primary electrical remodelling”. The abnormality of T wave in CM phenomenon is postulated to be the memory of myocardium that remembers the changes occurred during the abnormal depolarisation of pacing. Its rapid onset in humans is such that episodes of

abnormal ventricular activation as short as one minute in duration may exert lingering effects on repolarisation once normal ventricular activation has resumed.[93] The occurrence of cardiac memory represents significant remodeling of myocardial repolarization and occurs within minutes to hours of altered electrical activation (i.e. short-term memory). Furthermore, long periods of altered activation induce greater magnitude of T wave remodeling that persists for weeks to months (i.e. long-term memory).[94] This altered activation is thought to be able to induce adverse mechanical remodeling from dyssynchronous activation of the ventricle. Dyssynchronous activation reduces the mechanical efficiency of the ventricle and activates a cascade of signaling pathways that cause adverse structural remodelling.[95]

In the MOST Trial, it is demonstrated that RV pacing >40% potentially increased risk of heart failure hospitalization and incident atrial fibrillation three-fold compared to values below 40%. Nevertheless, few studies showed the possibility of PICM development, event in patients with pacing percetages between 20% and 40%.[96] Based on these results, clinicians should be vigilant to the possibility of PICM at lower pacing burdens.

1.7.3. Atrial fibrillation

Similar to the electrical and structural remodelling for cardiomyopathy, the presence of inter- and intraventricular asynchrony potentially plays a role in the development of atrial fibrillation (AF), by causing atrial remodelling. The mechanical effect of retrograde conduction causes an increase in atrial pressure and regurgitation into pulmonary vein, which may induce atrial fibrillation (AF). Even in no retrograde conduction is present, interference between sinus rate and VVI pacing rate leads to a periodicity of P-waves appearing after ventricular pace, mimicking retrograde conduction. This phenomenon will lead to pulmonary vein distention

and be a potent trigger in initiating AF.[91] Figure 3 showed the summary of structural remodelling after ventricular pacing.

The effects rapid atrial pacing in atrial electrical remodelling have been investigated extensively. Morillo et al demonstrated that electrical remodeling produces significant changes in AF inducibility after rapid atrial pacing.[97] At baseline, sustained AF could not be induced, whereas, after 6 weeks of chronic rapid pacing (400 bpm), the atrial refractory period shortened significantly and programmed electrical stimulation induced sustained AF in half (11/22) of the dogs. Electrical remodeling in atria affects atrial repolarization, which, in turn, alters the susceptibility to atrial arrhythmias.

Atrial electrical remodeling is associated with changes in ion channels at the cellular level. Atrial myocytes isolated from electrically remodeled hearts have exhibited a marked reduction in the transient outward potassium current (I_{to}), sustained outward current (I_{Ksus}) , and L-type calcium current ($I_{Ca(L)}$). These ionic changes likely account for the observed changes in atrial repolarization. However, the fundamental mechanisms responsible for triggering changes in channel expression in response to alterations in rate and activation sequence are poorly understood.

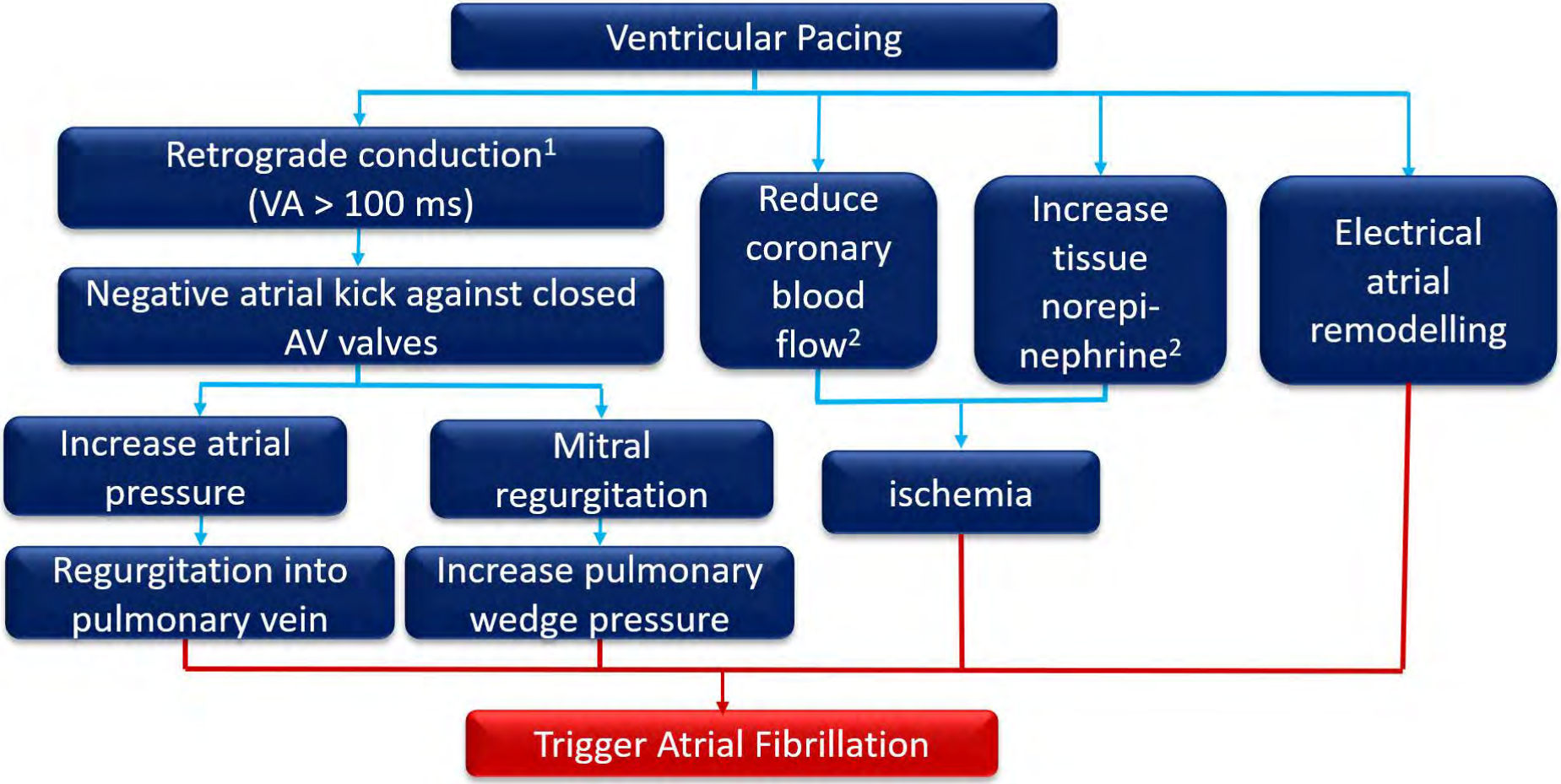


Figure 3. *Pathophysiology of ventricular pacing induced atrial fibrillation*

The relationship between normal atrial pacing and AF is not presently known given the lack of consistent data from randomized trials. There are some clinical data that suggest AF prevention with atrial pacing, and several clinical trials have shown that atrial or dual-chamber pacing in patients with bradycardia reduces the incidence of AF.[98] However, since majority of atrial leads are positioned in the RA appendage (RAA), it is possible that stimulation in this site results in delayed activation of areas of the atria. One important factor predisposing to re-entry is an increased dispersion of atrial refractoriness. RAA pacing could increase total atrial activation that might lead to dispersion of atrial refractoriness and important in the initiation of PAF.[99,100]

1.8.Device Algorithm to Prevent Atrial Fibrillation

1.8.1. Algorithms to minimize ventricular pacing

1.8.1.1.AV Search Hysteresis

The evidence of detrimental effects of chronic right ventricular pacing lead to the development of algorithms to reduce unnecessary ventricular pacing, as standard programming with physiologic AV interval usually causes unnecessary. AV search hysteresis (AVSH) is one of approach in dual chamber pacemaker aimed to promote physiologic rhythm in patients with intact or intermittent AV conduction. During 1:1 AV conduction (normal or prolonged P-R interval), this feature gradually prolongs the programmed AV delay in order to maintain intrinsic conduction and minimize numbers of ventricular pacing.

a. Abbott/StJude Medical

Ventricular intrinsic preference algorithm (VIP) is an AVSH algorithm from Abbott/StJude Medical. If the algorithm is activated, the device periodically extends sensed AV (SAV) and the paced AV (PAV) delay by a programmable value for the number of programmed search cycles to search for intrinsic conduction. Additionally, when three consecutive R-waves occur

at the programmed SAV or PAV delays, VIP will extend the SAV/PAV delays by the programmed value. If an R-wave is sensed during the extended AV delay, the ventricular pulse is inhibited and the SAV/PAV delays will remain extended until VP occurs. Extended AV intervals are allowed (up to three cycles in the study) when VP occurs before returning to basic AV delays. With VIP algorithm SAV/PAV delays are limited to a maximum of 350 ms, and VIP will not increase the delay beyond the maximum value. For example, when the PAV delay was set to 200 ms, the maximum available VIP setting was 150 ms. If a number of cycles (based on programmable settings) of absent ventricular sensed events is present (ie, continuous need for ventricular pacing), the algorithm will be deactivated.[101]

b. Biotronik (Intrinsic Rhythm Support (IRSplus))

IRSplus algorithm by Biotronik promote physiological conduction with a periodic AV conduction search every 180 cardiac cycles and operated with a basic AV delay of 225 ms and a rate-independent extended AV delay of 300 ms for both paced and sensed atrial events. The limit of 300 ms was deemed to be a good compromise for maximum AV delay. If VS is detected in 1 of 5 cycles, hysteresis is continued. However, if no VS detected, the device will be programmed back to short AV delay. After 180 beats of pacing cycles, there will be automatic extension in AV delay.[102]

c. Boston Scientific (AV Search Algorithm (AVSH)

When the AVSH feature is enabled, the AV Delay (either fixed or Dynamic) is periodically lengthened for up to 8 consecutive cardiac cycles to search for intrinsic P-R intervals that are longer than the programmed AV Delay. The AV Delay is lengthened by the programmed percentage AV Increase, and once increased, will remain extended as long as ventricular sensing is occurring. The pacemaker will revert to the programmed paced AV Delay following

the first ventricular pace at the Hysteresis AV Delay, or when the 8-cycle search window expires without sensing intrinsic ventricular activity.[103]

d. Medtronic (Search AV+)

Search AV algorithm operates in DDD/R mode with automatic extension of AV interval. The search AV operates in DDD/R mode as well as in DDI/R, DVI/R, or VDD mode with automatic extension of PAV and SAV interval. If AV conduction is not found within the range of maximally extended AV intervals, the device reverts to the programmed AV intervals and suspends search AV operations for progressively longer periods. The pacemaker assesses the 16 most recent AV conduction sequences and adapts the operating SAV and PAV intervals to the observed conduction time (either lengthens the operating SAV and PAV intervals by 62 ms for the next 16 pacing cycles to promote intrinsic conduction or shortens the operating SAV and PAV intervals by 8 ms for the next 16 pacing cycles). The maximum amount of time by which the SAV and PAV can be lengthened is limited by the Search AV+ Maximum Increase to AV parameter.[104,105]

1.8.1.2.Evidence of AV Search Hysteresis Algorithm

AV hysteresis algorithm is shown to be successful to reduce VP%. Previous study showed that activation of VIP algorithm could reduce the mean %VP at 12 months from 51.8% to 9.6% in patients with intact AV conduction, and from 78.9% to 28% in patients with underlying AV nodal disease.[101] To date, no evidence provided to support the significant benefit of the use of this algorithm in term of HF and AF reduction.[102,106] In light of these findings that prolonged intrinsic AV interval is associated with the risk of AF.[107,108]

1.8.1.3.AAI-DDD mode switch algorithm

The alternate strategy to reduce unnecessary ventricular rhythm is AAI-DDD mode switch algorithm, which essentially maintain the programming in AAI mode if ventricular intrinsic rhythm is detected, and switch to DDD mode if the one of the switch criteria is fulfilled. This algorithm is proved to be more reliable to achieve low ventricular pacing number compared to AV hysteresis algorithm.

a. Biotronik (VP Supression)

In ADI(R) mode, intrinsic conduction is monitored within a 450 ms interval after each atrial event. A cycle without intrinsic ventricular conduction triggers a further 8-cycle evaluation period. If any of the following criteria are met, the device reverts to DDD(R):

- 2 consecutive cycles without intrinsic ventricular conduction
- a programmable number (1–8) out of 8 cycles without intrinsic conduction
- no VS event for 2 or more seconds

If the long PR interval is shorter than 450 ms, the pacemaker will not switch to DDD.

b. Boston Scientific (RYTHMIQ^{TM})

Atrial-based pacing in AAI(R) with VVI backup (LRL minus 15/min), the 2 modes operate independently from one another. If complete AVB occurs, ventricular pacing will be delivered at backup VVI rate, asynchronous to the AAI rate. If 3 slow ventricular beats are detected in a window of 11 beats, AV conduction is considered blocked and switch to DDD(R) takes place. The algorithm will switch back to AAI if intact AV conduction is recuperated.

c. Medtronic (Managed Ventricular Pacing/MVP™)

MVP is an atrial-based pacing mode that is designed to switch to a dual-chamber pacing mode in the presence of AV block. If AV conduction is intact, the device remains in AAIR or AAI mode. While operating in AAI or AAIR mode, the parameters associated with single chamber atrial pacing are applicable. If 2 of the 4 most recent A-A intervals are missing a ventricular event, the device identifies a loss of AV conduction and switches to the DDDR or DDD mode. The device provides back-up ventricular pacing in response to dropped ventricular events until the loss of AV conduction is identified. After switching to DDDR or DDD mode, the device periodically checks AV conduction for an opportunity to return to AAIR or AAI mode. The first AV conduction check occurs 1 min after switching to DDDR or DDD mode. During the conduction check, the device switches to AAIR or AAI pacing mode for one cycle. If the next A-A interval includes a sensed ventricular beat, the conduction check succeeds. The device remains in AAIR or AAI pacing mode. If the next A-A interval does not include a sensed ventricular beat, the conduction check fails, and the device switches back to the DDDR or DDD mode. The time between conduction checks doubles (2, 4, 8 … min, up to a maximum of 16 hours) with each failed conduction check.[109]

d. Microport/Sorin (AAISafer™)

Atrial-based pacing in AAI (R). Switch to DDD(R) in response to any of the following:

- AAI to DDD switch on 6 consecutive PR intervals longer than the programmed long PR limit (AVB I criteria). The allowed duration of PR varies with the heart rate. In addition, the maximum allowed duration of PR intervals is programmable (physicians' choice)
- 3/12 non conducted atrial events (AVB II criteria)

- 2 consecutive non conducted atrial event (AVB III criteria), ventricular pauses of 2–4 s (programmable)

After 100 consecutive ventricular pacing, the device will check intrinsic AV conduction automatically. If 12 spontaneous ventricular beat detected, it will be switched back to AAI mode.

1.8.1.4.Evidence of AAI-DDD algorithm (MVP algorithm)

The use of automatic switching of AAIR-DDDR modes have been shown to be more effective in reducing %VP than standard AVSH algorithms in patients with both intact and compromised AV conduction and with intermittent AV block.[110,111] Murakami et al. reported the results of the Medtronic-sponsored IDEAL RVP study. This study compared Medtronic's AV Hysteresis algorithm (Search AV+) with their MVP algorithm. As both algorithms were available in the Medtronic Adapta® dual-chamber pacemaker, this was a within-patient, randomized, crossover-designed study where each mode was engaged for 1 month. The specific end result was the percentage of ventricular pacing. The net results showed single-digit percentages of ventricular pacing in the MVP mode, whereas there was a significantly higher percentage of ventricular pacing in the Search AV+ mode.[112]

The importance of this algorithm in clinical settings is associated with a reduction in the outcome of heart failure hospitalisation and atrial fibrillation related to a reduction in ventricular pacing. SavePACE trial was the first randomised control trial that evaluated the benefit of this algorithm as compared to conventional DDD settings. This study conferred a 4.8% absolute reduction in risk, which yielded a 40% reduction in the relative risk of the development of persistent atrial fibrillation.[106] Similar evidence shown by long-MinVPACE study, MVP algorithm seemed to reduce the risk of persistent AF occurrence from 42 % in

DDD group to 9% in intervention group.[113] Notwithstanding these evidence, in the latest RCT, MINERVA trial, MVP algorithm only did not show to give any significant benefit in the reduction of primary composite endpoints (including deat, cardiovascular hospitalisation, and permanent AF) as compared to conventional DDD. This study demonstrated that significant reduction of the primary composite endpoint could be achieved by the group with additional APP and aATP (DDDRP+MVP).[45]

1.8.2. Atrial Preventative Algorithms

Several electrophysiological mechanisms that can initiate and perpetuate atrial fibrillation (AF). Guyomar et al showed the evidence from pacemaker recording that the majority of episodes of paroxysmal AF are initiated by premature atrial complexes (PACs), by bradycardia or are due to immediate reinitiation of AF (IRAF).[114] Atrial preventative algorithms are designed based on idea that control of atrial rate may prevent the arrhythmogenic consequences of bradycardia and overdrive suppression of PACs may prevent the initiation of arrhythmia. Suppression of compensatory pauses or "short–long–short" cycles may reduce also arrhythmia onsets.

1.8.2.1.Atrial overdrive algorithm

Several manufacturers currently provide devices specifically targeted to patients at risk of recurrent paroxysmal AF. Since firstly described by Murgatroyd et al in 1994,[115] the overdrive pacing algorithm is the most commonly used algorithm for AF prevention, and available across all manufacturers. This algorithm adjusts the atrial pacing rate to just above the underlying intrinsic rhythm in such a way that the atrium is paced for at least 95% of the time (figure 4).[116]

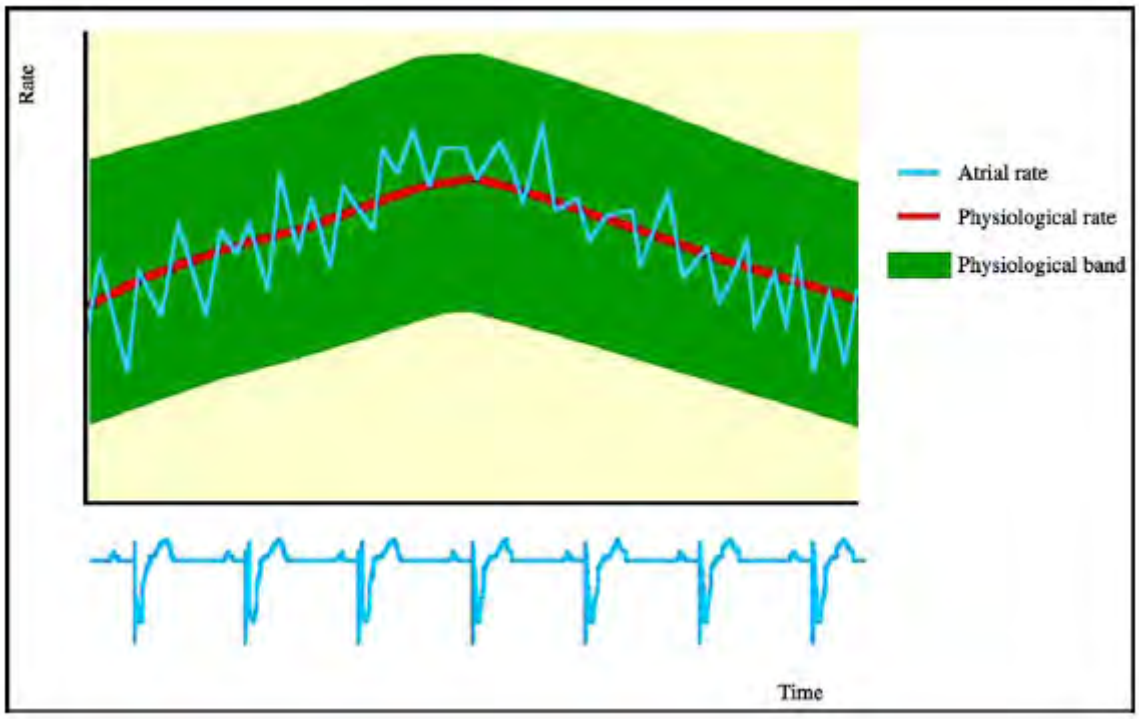


Figure 4. Atrial overdrive algorithm. The green zone shows physiological band, a zone of 15 bpm above and below the physiological heart rate (reproduced with permission from Mitchel et al, 2004)[116]

The details of each algorithm based on each manufacturer are described as follow:

a. Abbott/StJude Medical (AF Supression™)

StJude Medical devices provide AF Supression algorithm that override intrinsic atrial rhythm. The algorithm increased the pacing rate when two intrinsic atrial events were detected within 16 cycles. Four discrete programmable algorithm components controlled the overdrive pacing rate, the duration of overdrive pacing, and the rate at which the pacing rate decreases after an episode of overdrive pacing. The lower rate overdrive (LRO) defined the number of beats/min that the algorithm increased the pacing rate if the intrinsic rate was between 45 and 59 beats/min. Upper rate overdrive (URO) determined the number of beats/min that the algorithm increased the paced rate when the intrinsic rate exceeded 150 beats/min. The increase in overdrive rate between LRO and URO was based on a sliding scale between these two. Once stable pacing was achieved, the system continued to pace at the overdrive rate for a programmable number of cycles. If, during a period of overdrive pacing, additional intrinsic P waves were detected,

the algorithm increased the pacing rate again. If no intrinsic P waves were detected during the overdrive pacing period, the algorithm progressively extended the interval between successive atrial paced complexes, gradually slowing the effective pacing rate to either the programmed base rate or the sensor-defined rate. The recovery rate was the fourth parameter in the algorithm. It defined the cycle length increase on successive cycles. Two values were provided, separated by a colon. The first and second values identified the millisecond increase in cycle length, when the pacing rate was above and below 100 ppm, respectively.[117]

b. Biotronik (DDD+)

Atrial overdrive algorithm by Biotronik is achieved by completely suppressing any spontaneous atrial event in the range from the basic rate up to the maximum overdrive rate. This algorithm is similar to other persistent overdrive algorithms: basically, after every atrial sensed event (non-AES), the pacing rate is increased by a fixed rate increase (8 ppm) above the last P-P interval, until atrial events are no longer detected. If the intrinsic rate does not continue to rise after the programmable number of cycles (overdrive pacing plateau), the overdrive pacing rate is reduced in steps of 1 ppm, until an atrial sensed event is detected or the basic rate is reached.[118]

c. Boston Scientific (Atrial pacing preference (APP^{TM}))

The APP algorithm from Boston Scientific maintain a pacing rate slightly higher than the sinus rate with shortening pacing interval is shortened by 8ms if intrinsic P wave is detected. When the pacing state is maintained for search intervals (ie, 2–128 programmable cycles), the pacing interval is prolonged by 8 ms. The APP pacing rate is limited to the APP maximum pacing rate.[119]

d. Medtronic (Atrial preference pacing (APP^{TM}))

APP responds to changes in the atrial rate by accelerating the pacing rate until it reaches a steady paced rhythm that is slightly faster than the intrinsic rate, up to a programmed maximum rate. After each nonrefractory atrial sensed event, the device decreases the atrial pacing interval by the programmed Interval Decrement value. Beats continue at this elevated rate until the pacing rate exceeds the intrinsic rate, resulting in an atrial paced rhythm.

The increased rate is sustained for the number of beats programmed as the Search Beats parameter. APP then decreases the pacing rate slightly (by 20 milliseconds; nonprogrammable) to search for the next intrinsic beat. This results in a dynamic, controlled, stairstep increase or decrease in the pacing interval, maintaining a pacing rate slightly above the intrinsic rate.

e. **Microport/Sorin (Sinus Rhythm Overdrive (SRO)**

Sinus rhythm overdrive (SRO) was achieved by pacing at an interval 50 ms shorter than any sensed (non-premature) sinus cycle. SRO features a specific window designed to discard atrial events that might induce undesirably steep accelerations. Atrial events sensed in this window are considered non-sinus and do not induce acceleration. Following an accelerated plateau of 16 cycles, SRO gradually decreases in rate until sensing a new sinus beat. SRO conception allowed dynamic adaptation to exercise or to any other variations in sinus rate, but this function is immediately inhibited on sensing the onset of ATA, and reactivated on sensing its termination.[120]

1.8.2.2. Other atrial preventative algorithms

Apart from overdrive pacing algorithm, other atrial preventative therapies include all algorithms that aim in suppressing premature atrial complexes (PAC) triggers. Of all

manufacturers, these algorithms are only available in the Medtronic and Microport/Sorin devices.

Medtronic company equips their devices with atrial rate stabilisation (ARS) that aim to inhibit short-long-short interval after PAC. This algorithm prevents pauses after PACs by controlling the atrial rate in the two beats after PAC with gradually longer interval (figure 5a). Post made-switch overdrive pacing (PMOP) was developed based on occurrence of atrial tachyarrhythmia immediate after termination of AF (IRAF). The PMOP algorithm attempts to prevent these episodes by high rate pacing immediately after the end of the preceding arrhythmia, with A-A interval shortened by 15 ms until reaching the programming overdrive rate (figure 5b).[116]

Microport/Sorin devices provide post-extrasystolic pause suppression (PEPS) to prevent the occurrence of prolonged post extrasystolic pauses. Similar to ARS algorithm, if PACs is detected (defined as a spontaneous event approximately 25% shorter than the ongoing rhythm), the device delivers either: (1) an early AV pacing sequence after a premature atrial event, or (2) an early synchronous atrial pacing pulse when a premature ventricular event is sensed. PEPS is inactivated during ongoing atrial tachyarrhythmias.[116] Acceleration after premature atrial complexes (APAC) increases the atrial pacing rate by 5 bpm when repetitive premature atrial complexes (PAC) are detected. Successive accelerations are allowed until PAC disappearance or until an increment of 25 bpm higher than the previously ongoing rate was reached. Upon PAC disappearance, the atrial pacing rate remains at a plateau during 24 cycles, before gradually returning to the ongoing sinus rate. APAC is automatically inactivated if the pacing rate increase results in an increase in PAC frequency (figure 5c).[116,120]

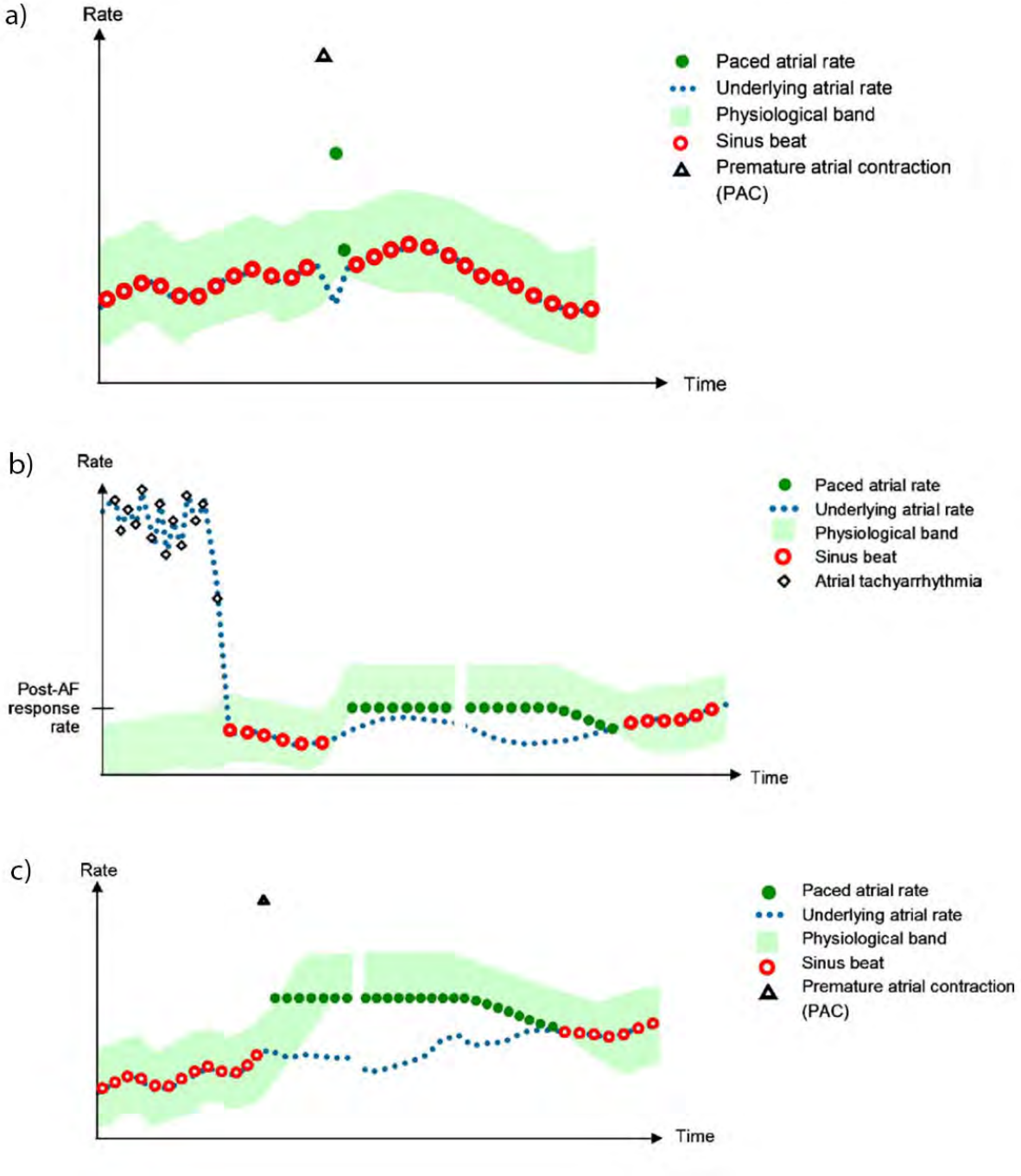


Figure 5. Other atrial preventative algorithms. (a) Atrial rate stabilisation (ARS) and post-extrasystolic pause suppression (PEPS). After a premature atrial contraction the paced atrial rate increased for the one beat and then reverts to the physiological rate (b) Post mode-switch overdrive pacing (PMOP) (c) Acceleration after premature atrial complexes (APAC). Period of sinus rhythm is followed by a premature atrial contraction. The atrial rate is increased by 15 bpm for 600 beats then gradually slows by 1 bpm every 16 beats (reproduced with permission from Mitchel et al, 2004)[116]

1.8.2.3. Evidence of atrial preventative algorithms

Several studies in the past investigating atrial preventive therapies showed contradictory results.[121-125] The earlier data from an RCT, ADOPT trial, showed that overdrive atrial pacing with the AF Suppression Algorithm decreased symptomatic AF burden significantly in patients with sick sinus syndrome and AF. The decrease in relative AF burden was substantial (25%), although the absolute difference was small (2.50% control vs. 1.87% treatment).[125] Similar evidence demonstrated in SAFARI trial, which showed less AF burden in the algorithm group at 3.7 hours/day vs 2.4 hours per day in APP vs DDD, respectively.[126] On the other hand, contradictory results were shower by the two more recent trials, SAFE and ASSERT studies. [122,127] These trials did not seem to show find a substantial benefit of continuous atrial overdrive pacing in preventing AF occurrence. In ASSERT trial, 2451 pacemaker patients randomized to continuous atrial overdrive and standard DDD groups. This study revealed no difference in the annual rate of atrial tachyarrhythmia development (1.96 percent per year in patients randomized to receive atrial overdrive pacing versus 1.44 percent per year in control patients) and no difference in the combined end point of stroke, systemic embolism, myocardial infarction, death from vascular causes, or hospitalization for heart failure.[121] Likewise, SAFE study that enrolled 385 patients also showed that continuous atrial overdrive pacing did not prevent the development of persistent AF .[122]

1.9.Device Algorithm to Terminate Atrial Fibrillation (Atrial Antitachycardia Pacing (aATP) Algorithm)

1.9.1. Details of atrial antitachycardia pacing algorithm

The idea that early termination of atrial tachyarrhythmias may limit atrial remodelling lead to the development of aATP algorithm. If the device detects an atrial tachyarrhythmia (AT) episode, aATP therapy will be delivered at an atrial cycle length shorter than the interval of

arrhythmia detected, in order to access the re-entrant circuit during any excitable gap and to extinguish the arrhythmia. Based on this, successful therapy application is therefore limited to AF patients who have a history of atrial flutter or show intermittently more organized atrial macroreentrant tachycardias susceptible to aATP. Treatments for such episodes are intended to interrupt the atrial tachycardia and restore patient's normal sinus rhythm.

The device can deliver up to 3 aATP therapies to treat an AT/AF or a Fast AT/AF episode. In older generation, aATP therapies become available when the duration of sustained atrial tachyarrhythmias exceeds the programmed value of episode duration before aATP delivery (Time-interval). However, newer generation of aATP therapy, reactive ATP™, allows for multiple deliveries of programmed aATP therapies during an atrial tachyarrhythmia episode, not only attempt atrial tachyarrhythmia termination after detection, but also watch for any change in the rate or regularity and then opportunistically apply aATP therapy when the episode is most vulnerable to pace termination. When an AT/AF or Fast AT/AF episode is detected, the device delivers the first sequence of the ATP therapy. After the first ATP sequence, it continues to monitor for the presence of the atrial tachycardia episode. If it redetects the atrial tachycardia episode, the device and repeats this cycle until the episode is terminated or all sequences in the therapy are exhausted.

Atrial ATP therapy consist of two types:

- Atrial ramp

  Ramp therapy sequences consist of a programmable number of AOO pulses delivered at decreasing intervals. VVI ventricular backup pacing is available during Ramp pacing. The first pulse of each Ramp sequence is delivered at a programmable percentage of the current

atrial cycle length (the median of the last 12 P-P intervals). The rest of each sequence is delivered at progressively shorter intervals, based on the programmed Interval Decrement.

- Atrial burst+

  Burst+ therapy sequences consist of a programmed number of atrial pulses at a chosen percentage of the AT cycle length, followed by 2 premature stimuli that are delivered at shorter intervals. VVI ventricular backup pacing is available during Burst+ pacing. The AOO sequence is delivered at the programmed A-S1 Interval timed from the first sensed A-event following the V-event that fulfills detection. The first premature stimulus is delivered at the S1-S2 percentage. The second premature stimulus is delivered at the S1-S2 interval minus the programmed S2-S3 Decrement.

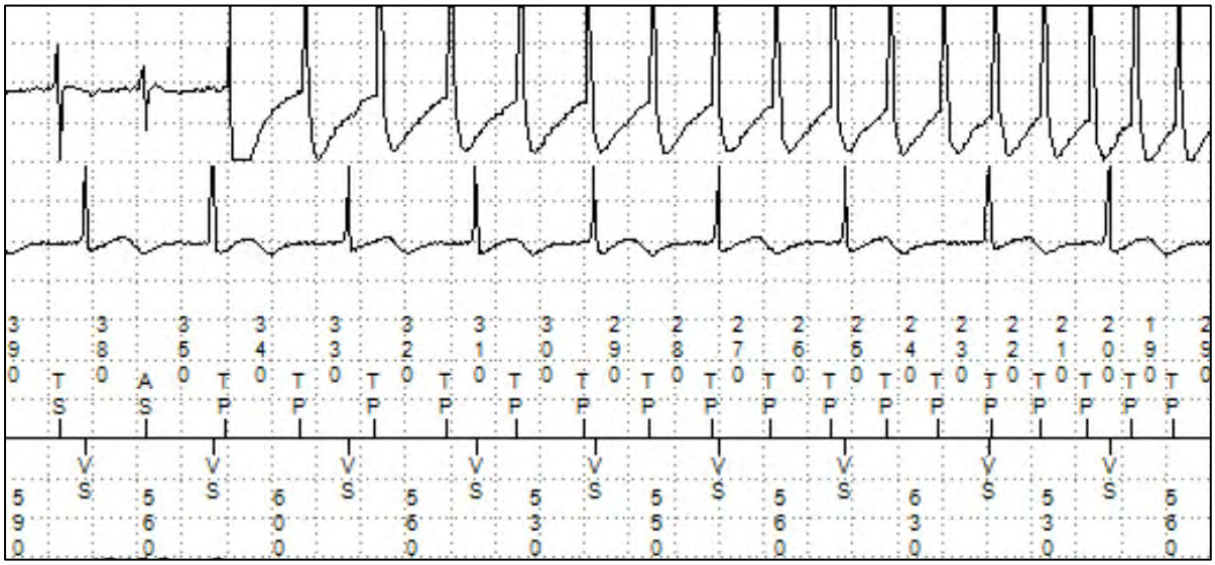
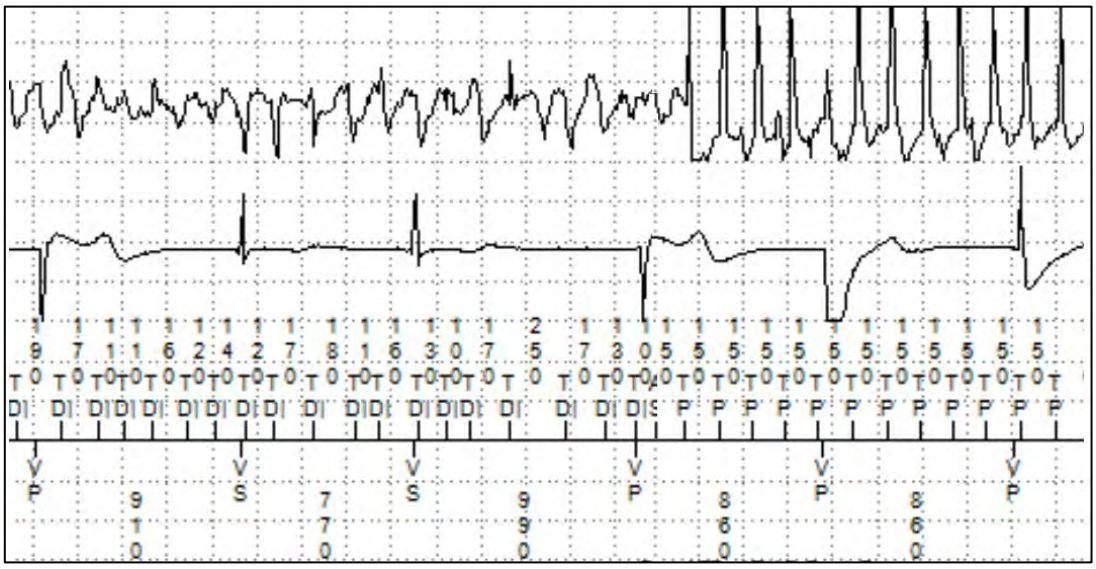


Figure 6. Example of Ramp sequence in aATP therapy



- **Figure 7**. Example of Burst+ sequence in aATP therapy

1.9.2. Evidence of atrial antitachycardia pacing algorithm

Many clinical trials have been conducted over the past 10 years investigating aATP algorithm for AF termination. Gillis et al. in 2009 reported the first long-term data on aATP, showing neither ATP alone nor ATP+APP algorithms could successfully suppress atrial tachycardia (AT)/AF during a follow-up period of 3 years. In all these trials, ATP correlated to moderate efficacy in terminating slow regular ATs, low efficacy in terminating fast regular AT, and was ineffective in established AF.[128] These findings correspond to the results of other aATP trial such as ATTEST and FACET trials.[124,129]

The latest RCT published, MINERVA study, demonstrated that aATP can decrease the burden of AF, between the group of DDDR vs. MVP vs. DDDRP+MVP with 17 vs. 9 vs. 4 minutes/day, respectively. In addition, DDDRP+MVP was also associated with a 48% relative risk reduction in progression to persistent or permanent AF over 2 years and a 52% reduction in AF-related hospitalizations and emergency visits.[45] In this study, the impact of aATP may

seemed to be higher in comparison with previous studies. It is possibly related to the new feature of aATP (Reactive ATP) which allows the device not only attempts atrial tachyarrhythmia termination after detection but also watches for any change in the rate or regularity and then opportunistically applies aATP therapy when the episode is most vulnerable to pace termination. The use of Ramp, rather than Burst+, as the first aATP therapy may have improved the efficacy of atrial tachyarrhythmias termination in comparison with previous studies.[130]

1.9.3. Atrial antitachycardia pacing algorithm in patients post AF ablation

In patients with persistent AF, pulmonary vein isolation (PVI) is still the mainstay of ablation treatment, however the success rate of PVI alone remained suboptimal. Despite advanced techniques used in performing radiofrequency ablation (RFA) of AF, this procedure results in regular atrial tachycardias (ATs) or atrial flutter (AFl), which is one of the most important proarrhythmic complication.

Incidence of AT/AFl related to AF RFA reported to be variable, depending on the method and extent of the ablation. The occurrence of ATs after segmental pulmonary vein (PV) isolation was found to be ranging between 1% and 2.9%.[131,132] If PV ablation was achieved by placing circular lesions around the veins in the LA antrum and creating additional lines in LA (such as mitral isthmus, and/or roof, or posterior lines), the incidence of ATs will be dramatically increased, ranging from 10% to 24 %, around 10 fold higher than straight forward PV isolation.[133,134]

To date, there was no evidence published with regards to the use of the aATP therapy particularly in posft AF ablation patiets. Notwithstanding the fact that aATP alone showed low efficacy in terminating fast regular AT and ineffective in established AF, previous trials supported that aATP is correlated to moderate efficacy in terminating slow regular ATs,.[128]

1.10. Magnetic resonance imaging in cardiac implantable electronic devices

1.10.1. Principle of MRI in cardiac implantable electronic devices

MRI scans essentially map the location of hydrogen nuclei that is abundance in the body in the form of water and fat to generate the images of anatomy of interest. An MRI image results from a tomography map of proton distribution in the image sample and influenced by the difference in the ability of targeted organ to re-emit the absorbed radiofrequency signal and flow phenomena. To perform this action, MRI requires a static magnetic field (measured in Tesla [T]), pulse gradient field (measured in T per meter per second), and radiofrequency field (measured by specific absorption rate [SAR] in watts per kilogram). The magnets used for the procedure typically range from 0.2 T to 9 T, which equivalent to 4,000 to 60,000 times greater than Earth's magnetic field. These fields, alone or in combination, can interact with come metallic objects as well as potentially damage the performance of electronic components.

1.10.2. Potential hazards of the interactions between conventional pacemakers and the MRI environment

According to 2017 HRS Expert Consensus on MRI and Radiation Exposure in Patients with CIEDs, MRI non-conditional include all system that do not meet MRI-conditional labelling criteria, which pose a known hazard in the MRI environment or combination of devices not specifically tested together for conditional labelling.[135] This includes MR conditional generators that have been combined with non-conditional leads, combination of individual MR

conditional lead and device components from different manufacturers, or MR conditional systems implanted in patients that do not meet all specific conditions of use, such as patients with abandoned leads.

Few potential hazards caused by electromagnetic interference from MRI have been published. Some of the fatal safety concerns, notably deaths immediately after MRI procedure, were not found in all included studies in this meta-analysis. This was the opposite of previous publication that reported death attributed to MRI scans.[136] However, this report are now known to be poorly characterised (unmonitored patient and mechanism of death is not confirmed). Other potential hazards in the non-conditional CIED include the following:

1.10.2.1. Effects of MRI exposure to CIED leads

RF fields produce high currents that results in the heating of the lead tip and subsequently cause injury of the surrounding myocardial tissue. In the in vitro experiment, it is showed various temperature increases with the maximum of 40℃ was notable, resulting in the increase of stimulation threshold and impedance.[136,137] Our study shows a low incidence of CIED parameter changes either in threshold, low voltage impedance, or P and R wave amplitude, implying no significant myocardial injury related to this procedure. The major reason the leads do not heat up in vivo is likely due to the cooling effect of blood flow through the heart tissue and around the lead tip-tissue interface. Furthermore, heating effects is known to be more dependent to the lead position within the MRI unit in the direction to the main magnetic field. However, we found that the incidence of high voltage impedance rising is much higher, at around 23%. This was unexpected as the conductors for shock coils are structurally stronger than pacing-sensing conductors in order to deliver strong currents, and thus the incidence of isolated fracture of high-voltage conductor is lower than to that of pacing/sensing conductor. Nonetheless, most of the included studies disclosed a cut-off point of >3Ω, which is likely not

clinically relevant. Limited data has shown that lead fractures were highly indicated in the evidence of an abrupt impedance increase >75% or >100 ohm.[138] Notably, none of the patients who experienced changes in the parameter either in low voltage leads or high voltage leads in this meta-analysis reported to have immediate replacement related to this outcome.

Furthermore, the gradient magnetic and radiofrequency fields may cause “antenna effects” that results in the electric current to conduct to the lead tip, and possibly induce rapid capture and stimulation of the myocardium, which might trigger dangerous arrhythmias. In addition to that, induced electrical currents may also mimic intrinsic cardiac signal, which results in oversensing or under-sensing. Magnetohydrodynamic effect results from conductive effect of blood may cause T-wave oversensing which lead to inhibition of pacing in CIED or false recognition of atrial or ventricular arrhythmia.[139] In ICDs, this may result in inappropriate tachycardia or shock therapy. Notably, while therapy delivery during MRI is not possible because of saturation in the magnetic field, permanent device failure might still happen after a given number of unsuccessful attempts to charge capacitor.[140] This emphasizes that deactivation of tachyarrhythmia therapies before procedure is a mandatory.

1.10.2.2. MRI exposure to generator

CIED generators contain ferromagnetic materials that are present in the batteries and reed switches, therefore mechanical movement due to magnetic force during MRI could occur and CIED generator may be displaced. As a result, patients may complain of significant pulling or torque sensation during MRI. However, this issue has proven to be unjustified because the ferromagnetic contents is very low in the newer PPM generation. Similarly, despite a higher content of ferromagnetic content is found in the ICD generators, the movement impact related to MRI is still unlikely to be clinically significant.[141] Additionally, there are no significant

ferromagnetic materials contained in the leads, therefore lead movement is not expected to occur in a magnetic field.

1.10.2.3. Device programming

Changing in the programming parameters during MRI is also a concern when a CIED is brought close to MR scanner. Older devices have magnet-activated reed switch that can be activated with externally. When reed switch is activated, asynchronous pacing occurs at magnet rate and tachycardia therapy is disabled. Reed switch activation is aimed to prevent any interference during electrocautery surgery. However, in this case there is a substantial risk for ventricular fibrillation, particularly in patients with unstable condition such as myocardial ischemia. In addition, prolonged reed switch activation would also accelerate battery depletion.

The other programming dysfunction related to MRI is an electrical resetting, which reverts device program to factory default settings under an exposure of a strong magnetic field. This actually is a safety feature created by manufacturers to ensure the function of CIEDs under certain situations causing generator not functioning properly. However, in pacemaker dependent patients, this might result in asystole period. In our study, we found low incidence of electrical reset, with an incidence of 1.43%, and most likely not related to any fatal clinical consequences.

CHAPTER 2

Predicted Longevity of Contemporary Cardiac Implantable Electronic Devices: A Call for Industry-wide "Standardized" Reporting

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2.1. Introduction

The number of cardiac implantable electronic devices (CIEDs) implants has risen significantly over the last two decades, with greater proportional increase in implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy-defibrillator (CRT-D) over that of permanent pacemaker (PPM).[1,2] This can be attributed to the broadening indications for treating ventricular arrhythmias and preventing sudden cardiac death. Although the upfront cost associated with CIEDs implants is high, the cost-effectiveness of ICD and CRT-D devices is well established.[10]

Device longevity has been shown to have the largest impact on cost-effectiveness analysis of primary prevention ICD therapy. Recent modeling data suggests that extending device longevity from 5 to 9 years for ICDs and 4 to 7 years for CRT-Ds is associated with a 29 to 34% annual cost savings over a time horizon of 15 years.[142] Further, there is a mismatch between patient survival and device longevity of ICDs that results in significant clinical and economic burden.[143] This mismatch leads to an increased probability of generator change that confers up to a 4-fold increased risk of infection and up to 5-fold increased risk of lead complications.[144,145] Indeed, an increased burden of high voltage generator changes may in part contribute to the elevated infection incidence associated with CIED implants in recent years.[1]

Several investigators have reported on the differences in device longevity among CIED manufacturers and a 10-20% improvement in overall longevity in newer generation devices.[146-155] The utility of data from these retrospective studies are somewhat limited as the CIEDs are largely superseded by newer models and technology at the time of reporting, with some also noted to suffer from manufacturer selection bias. Nonetheless, information regarding CIEDs longevity are important to insurers, payers as well as clinicians. Therefore, we aimed to perform

a prospective comparison of predicted longevity of current generation CIEDs using best-matched CIEDs settings and modeling scenarios.

2.2. Methods

We included current model CIEDs from Medtronic, St Jude Medical, Boston Scientific, Biotronik and LivaNova that were available in Australia as of 31 March 2017. Predicted CIEDs longevity for all settings were extracted from respective manufacturer's product manuals along with battery chemistry, capacity, time from beginning of life (BOL) to elective replacement indicator (ERI) and pacemaker housekeeping current drain estimates. For ICD/CRT-D, we back calculated the standardized housekeeping current drain using the following equation: Housekeeping current drain [μA] = capacity (usable capacity [μAh])/Time (estimated longevity [hours]).[156] Where comparable data were unavailable, we approached the relevant manufacturer for additional estimations at the required standardized settings. All the data included in this report have been independently verified by the respective manufacturer.

2.2.1. Pacemakers

We included the following single (SR) and dual chamber (DR) PPM devices: Medtronic Advisa^{TM} and Ensura^{TM}; St. Jude Medical Assurity RF; Boston Scientific Accolade and Accolade EL; Biotronik Evia; LivaNova Kora 100. Two Boston Scientific sub-models (Accolade and Accolade EL) were assessed due to distinctly different battery chemistry, capacity and longevity. Data from 30 different modeling permutations were retrieved. The most prevalent pacing setting across manufacturers was: amplitude at 2.5V; pulse width at 0.4ms; impedance at 500ohm; pacing load at 50% or 100% and rate at 60bpm. Predicted longevity was derived at basic functionality with advanced features or algorithms turned on or off: rate-

response, remote monitoring, storage of pre-arrhythmia electrograms and anti-tachycardia pacing.

2.2.2. Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Devices

We included the following ICD/CRT-D devices: Medtronic Evera/Viva®, St. Jude Medical Fortify/Quadra, Boston Scientific Autogen EL and X4, Biotronik Iperia and LivaNova Platinium. The parameters for ICDs were chosen to represent a primary prevention scenario with 0% or 15% V pacing in SR ICD and both 15% A & V pacing in DR ICD, with zero clinical shocks. The parameters for CRT-Ds were set at 15% A & 100% bi-ventricular (Bi-V) pacing with zero clinical shocks. Pacing rate, output, pulse width and lead impedance were as follows: 60bpm, 2.5V, 0.4ms and 500Ohm respectively. Additionally, the following ancillary information were noted: number of essential capacitor/battery reforms; number of remote monitoring alerts and amount of time remote monitoring is active per year; and usage of radio frequency telemetry at device implant.

2.3. Results

2.3.1. Pacemakers

2.3.2.1. Battery chemistry, capacity and device size

All manufacturers use a lithium anode battery (Figure 1). Greatbatch Quasar medium rate batteries or lithium-carbon monofluoride or lithium-silver vanadium oxide (Li-CFx/SVO) chemistry are used at least partially in all companies with the exception of LivaNova and Boston Scientific, where previous generation lithium iodine (supplied by Greatbatch) and proprietary lithium-magnesium oxide (Li-MnO_2) batteries are used respectively. The median useable battery capacity taken from BOL to ERI or recommended replacement time (RRT) was 1.03 (IQR 0.91-1.10) Ah. The physical size of the pacemaker correlated with useable battery

capacity with the largest device at 15.8 cc (Boston Scientific DR Accolade EL; 1.6 Ah) and the smallest at 7.5 cc (LivaNova SR Kora 100; 0.81 Ah).

2.3.2.2. Housekeeping current drain

All manufacturers except for Boston Scientific disclosed the housekeeping current drain of their PPMs showing a range of 5.4µA (St. Jude Medical SR Assurity RF) to 10.3µA (Medtronic DR Advisa^{TM}) with a median of 6.5µA (Figure 1) at 100% inhibited, sensing at 60 bpm. Further, mean back calculated housekeeping current drain was lowest for St. Jude Medical Assurity and LivaNova Kora (8.9µA), while Medtronic Advisa^{TM} demonstrated the highest current drain (14.2µA) over all conditions assessed (50% and 100 % pacing; SR and DR, features on and off).

2.3.2.3. Predicted longevity

Predicted longevity with all features turned off were disclosed by all manufacturers except St Jude Medical. The mean predicted longevity of a SR PPM (with all advanced features turned off) at 50% and 100% pacing load was 13.0±1.8 and 11.6±1.5 years respectively (Figure 2A). Notably, the predicted longevity of St Jude Medical SR Assurity eclipsed all other manufacturers' estimates at 15.3 (50% pace) and 13.5 years (100 % pace) with advanced features turned on (Figure 2A & B). The mean predicted longevity of a DR PPM device (with all advanced features turned off) at 50% and 100% pacing load was 11.5±2.2 and 9.6±1.8years respectively (Figure 2C). The device with the longest projected longevity with advance features on at 50% and 100% pacing load were Boston Scientific DR Accolade EL at 12.4 years and at 10.9 years respectively (Figure 2C & D).

2.3.2.4. Impact of pacing burden and advanced features

Data from the four companies that provided longevity estimates with advanced features turned on and off showed a decline in longevity of 1.4 (range 0.5-3.6) years when all available advanced features such as blended rates response, remote monitoring and wireless telemetry were activated (Figure 1). Notably, Medtronic's extended pre-arrhythmia electrogram recording had the greatest potential impact on battery life at ~2.3 to 3 years (Figure 1). The greatest impact in projected longevity with increased pacing load from 50 to 100% was seen in PPM with smaller battery capacity and/or more efficient housekeeping current (averaged for SR/DR: LivaNova Kora 16%; Biotronik Evia 16%; St Jude Medical Assurity 14%; Boston Scientific Accolade EL 14% & Accolade 11%; Medtronic Advisa/Ensura^{TM} 10%).

2.3.2. ICD/CRT-Ds

2.3.2.1. Battery chemistry, capacity and device size

All manufacturers use, at least in part, a hybrid Li-CFx/SVO battery chemistry, except for Boston Scientific where proprietary Li-MnO_2 is used (Figure 3). Notably, Biotronik utilized a 50:50 split of both CFx and SVO chemistries in their ICD range. The volume of the VR device with DF-4 header ranged from 29.5cc (Boston Scientific Autogen EL) to 35cc (St Jude Medical Fortify). The median useable battery capacity was 1.31Ah to RRT or ERI and ranged from 1.0Ah (Medtronic Evera/Viva$^{®}$) to 1.78Ah (Boston Scientific Autogen EL).

2.3.2.2. Standardized housekeeping current drain

The housekeeping current drain of high voltage devices was not disclosed by any manufacturers. The LivaNova Platinium has the lowest mean back calculated standardized housekeeping current drain of 9.6/10.0 µA for SR/DR ICDs respectively (0% pace, annual capacitor reforms). The Boston Scientific Autogen and Biotronik Evia devices were associated

with the highest current drain at 16.0 and 16.1µA respectively. CRT-Ds (15% A, 100% Bi-V pacing, annual capacitor reforms) also demonstrated similar between manufacturer trend in housekeeping current drain with an overall mean of 18.7µA (ranging from a low 14.4µA for the LivaNova Platinium to a high 23.1µA for the Biotronik Iperia HF-T).

2.3.2.3. Predicted longevity

Under monitoring conditions (0% pace, essential capacitor reforms only, rate response sensor off) with radiofrequency remote communication and home monitoring on, the mean predicted longevity of a SR and DR ICD was 12.8±3.1 and 12.0±3.3 years respectively (Figures 4A & B). The mean predicted longevity of CRT-D devices (with 15% A and 100 % Bi-V pace at 60 bpm, 2.5 V, 0.40 ms; 500 Ohm leads, sensor off, RF remote communication and home monitoring on) was 8.8±2.1 years (Figure 4C). Under monitoring conditions, Boston Scientific, and LivaNova devices only require two capacitor/battery reforms per annum to maintain charge time due to the composition of their capacitors (Tantalum versus Aluminium). Although Medtronic devices do not require capacitor reform, 4 half energy charges per year are required for battery conditioning. Biotronik devices perform four full energy charges per year to maintain charge time of their capacitors, whilst St Jude Medical devices average 3 charges per year with more charges required as charge time increases when approaching ERI (Figure 3). The time to ERI or EOL was similar for most manufacturers with a 3-month safety period under varying conditions. Interestingly, the LivaNova Platinium provided the greatest safety margin of 11 months with eleven 34J charges. In contrast, Biotronik devices allow for 3 months with six 42J charges, whilst St Jude Medical devices allow for 3 months with three 42J charges (Figure 3).

2.3.2.4. Impact of pacing burden and advanced features

When a 15% pacing load (both chambers in DR devices) was applied to the ICDs, the median longevity reduced to 11.4 and 10.5 years for SR and DR devices, respectively (Figure 3). CRT optimization methodologies of multi-point pacing (MultiPoint™, St Jude Medical) and automatic AA & VV optimization (SonR™, LivaNova) were associated with a 1.2 and 1.1 years reduction in predicted longevity respectively at basic rate pacing with sensor off (Figure 3). Conversely, another RV-triggered adaptive CRT algorithm (AdaptivCRT™, Medtronic) improved longevity by 0.5 years via a modeled reduction in RV pacing (Figure 3).

2.4. Discussions

This study provides an up-to-date comparison of contemporary CIEDs' predicted longevity using best-matched device settings and modelling scenarios. In keeping with previous retrospective reports, we found significant variations in CIEDs longevity from different manufacturers with up to 44, 42 and 44% difference seen for PPMs, ICDs and CRT-Ds respectively. Specifically, our findings are as follows:

1. A maximum of 6.2 years difference between the best and worst predicted longevity for PPMs (SR device, 50% pace; features on);
2. Turning on advanced features such as blended rate response, pre-arrhythmia electrogram recording and radiofrequency remote monitoring can reduce PPM longevity by 0.5 to 3.6 years;
3. A maximum of 7.7 years difference between the best and worst predicted longevity for ICDs (SR device; 0% pace; capacitor reforms only; features on);
4. A maximum of 5.3 years difference between the best and worst predicted longevity for CRT-Ds (15% A pace; 100% Bi-V pace; capacitor reforms only; features on);

5. Turning on CRT optimization features such as MultiPoint™ and automatic AV & VV delay algorithm (SonR™) can reduce CRT-D longevity by up to 1.2 years while RV triggered adaptive CRT algorithm (AdaptivCRT™) can improve longevity by up to 0.5 years.

Therefore, careful selection of device manufacturer can help reduce the potential mismatch between patient survival and device longevity. This is more crucial for younger patients with longer expected lifespan where the potential to reduce or avoid the negative clinical and cost implications of future generator replacements is much higher.

2.4.1. Factors impacting CIEDs longevity

Previous retrospective real-world studies have found differences in device longevity according to manufacturers,[146-154] pacing lead parameters (pulse width, voltage, impedance), overall pacing burden and high-voltage therapies delivered.[49,146-149,151] Our data supports previous findings and highlights device battery capacity and housekeeping current as the most important factors that determine CIEDs longevity.[49,143,147] The current drain represents energy used for housekeeping functions, and the current used to pace the heart and sense the underlying rhythm.[156] A larger battery capacity is able to cater better to higher pacing demands and additional pacing features (e.g. Boston Scientific Accolade EL) while a lower housekeeping current drain is advantageous in scenarios with low pacing requirements (e.g. St Jude Medical Assurity). For high-voltage devices, the combination of large usable capacity and the most efficient back-calculated standardized current allows the LivaNova Platinium ICD/CRT-D range to excel in predicted longevity by up to 8 years (Figure 2). While all contemporary CIEDs utilize hybrid carbon mono-fluoride lithium based battery chemistry, the Li-MnO_2 (EnduraLife™) chemistry of Boston Scientific's ICD allows ERI triggering at ~90% of total capacity (due to a more stable internal battery resistance) in contrast to ~70% in the competitors' Li-CFx-SVO hybrid chemistries thus allowing the greatest usable capacity on the market, even

though it does not have the largest total capacity. Rapid high-voltage capacitor charge from an ICD shock event consumes a similar amount of battery energy from all manufacturers with slight dependence on the capacitance of the capacitor. However, due to differences in battery capacity, housekeeping current and pacing requirements, the relative impact on the longevity ranges from 16 [Boston Scientific CRT-D] to 47 days [Medtronic VR]) in the two manufacturers that disclosed these estimates in their manuals (Figure 2). It would be reasonable to estimate that each maximal energy shock would reduce longevity by roughly 1 month.

Over the past decades of CIEDs development, manufacturers have introduced different pacing algorithms and features with aim to improve clinical outcomes and device longevity. Ventricular auto-capture algorithms have been shown to extend longevity by up to 1.4 years compared with standard programming.[51] In a similar fashion, reducing the safety margin of left ventricular lead pacing amplitude to 0.5V has been shown to improve CRT longevity by 0.6 years.[157] Further, minimization of ventricular pacing in dual chamber devices via AAI-DDD algorithm has been shown to increase predicted longevity by 1.2 years versus DDD setting.[158] Similarly, AV delay extension (AV hysteresis) and sleep rate programming have been shown to result in ~0.8 and 0.3 year increase in predicted longevity.[49] In CRT devices, reduction of RV pacing using the AdaptivCRT™ (Medtronic) algorithm could result in improved longevity by up to 0.5 years. One study found that high impedance leads that reduce current drain could save up to 0.8 years of longevity.[49] Generally, the gain in device longevity through the programming of aforementioned algorithms could potentially be up to 1 year.

On the contrary, some algorithms that aim to optimize CRT response have been found to shorten battery longevity significantly although randomized controlled trial data remains limited. The MultiPoint™ pacing (St Jude Medical) trial demonstrated non-inferiority of

MultiPoint™ pacing to standard bi-v pacing in terms of safety and efficacy in treating heart failure.[159] Likewise, the RESPOND-CRT trial (SonR™, LivaNova) yielded equivalence in clinical response rate between automatic SonR™ contractility sensor and echocardiographic-guided optimization of the AV & VV timings although there was a 35% reduction in heart failure hospitalizations as a secondary endpoint.[160] Further, blended rate response available in both Boston Scientific and LivaNova devices has been found to restore chronotropic response at the expense of longevity, however, it was not associated with reduced death, heart failure hospitalization or stroke.[161] Finally, wireless remote monitoring of ICDs has shown comparable overall outcomes to in-office follow-up related to patient safety and survival.[162] Perhaps more rapid detection of clinical events, reduction in inappropriate shocks and potential survival benefit in those with daily transmission verification may justify the impact of remote monitoring on battery longevity.[162]

Taken together, gains in device longevity can be obtained via activating features like auto-threshold or those that reduce unnecessary pacing or conversely, via deactivating energy draining algorithms. Indeed, in the absence of robust hard endpoint data, algorithms that reduce longevity should only be used selectively and with clinical justification. If longevity was a key priority, selecting the appropriate device brand would yield much larger net gains in longevity than device programming. Ultimately, the selection of device brand would entail consideration of factors such as perceived brand reliability, availability of support service, device size, magnetic resonance imaging conditionality status, device warranty and patient's preference.[163]

2.4.2. Call for Standardized Reporting by CIEDs Manufacturers

In collating the available data pertaining to CIEDs predicted longevity, we found a distinct lack of standardized reporting by CIEDs manufacturers. Some pertinent information such as battery

capacity and chemistry are sometimes kept proprietary and undisclosed. Yet, longevity estimates are often included in the CIED marketing by manufacturers. The usage of different settings for deriving predicted longevity has been a significant impediment for payers, insurers, patients and physicians to gain a fair assessment of the differences between brands and models. Indeed, an industry-wide standardized reporting in predicted longevity for all CIED products is long overdue[163]

2.4.3. Study Limitations

Real-world longevities will differ from the predicted industry modelling due to departure of the underlying assumptions regarding pacing burden that may increase due to usage of beta-blockers, lead impedance/threshold, use of advanced features, electrogram recording requirements and number of ICD shocks delivered. Although accelerated CIEDs battery predictions almost always over-predict real-life longevity, the correlation is improved in newer generation devices.[154,155] Despite the likely overestimation, our data are aimed at investigating differences in longevity using standardized settings and hence, the relative differences between manufacturers should still hold true. The automated CIEDs reprogramming at ERI can be variable among the different CIEDs to result in loss of rate response or AV synchrony. The current comparison does not take into account the variable clinical management of patients with CIEDs approaching ERI. The current longevity comparisons are restricted to a single model per manufacturer. Even though new models are frequently released, the core battery/circuit board design is most often maintained and hence, our comparative estimates will likely remain valid in the absence of new battery chemistry or design. Differential tolerances in battery manufacture and decay characteristics may alter the predicted longevity of CIEDs although the standard deviation of these are likely to be small.

2.5. Conclusion

In contemporary CIEDs, predicted device longevity remains highly variable among the different manufacturers. CIEDs longevity remains an important factor that can impact on healthcare costs as well as clinical outcomes in the settings of future need for generator replacements. Industry-wide standardized reporting of predicted CIEDs longevity is urgently required.

2.6. Figures

Figure 1: Physical characteristics, features and predicted longevities of PPMs. All estimates are 2.5V; 0.40 ms, 60 bpm, 500 Ohm lead with IEGMS at least partially on. ACC=Accelerometer; CLS=Closed loop stimulation; DR=Dual chamber; HM=Remote monitoring via automatic RF telemetry; MV=Minute Ventilation; NA=Not available RF=Radiofrequency; RM=Remote monitoring via patient initiated inductive telemetry; SR=Single chamber; Yrs=Years; *=BOL; 100% inhibition; **=Features off conditions. Allows for no home monitoring, no RF transmission time (if available), no rate response monitoring and no EGM or pre-EGM recording (if programmable); A=Average capacity between Litronik and Greatbatch cells; B=Inductive (wanded) remote monitoring only; negligible impact on battery; C=Calculated longevity was estimated using a programmed pulse width of 0.35ms, which is equivalent to a delivered value of 0.366ms. Adjusted longevity was calculated by subtracting 6 months from longevity to account for zero shelf-life estimate; D=Daily check, 12 FU per annum; E=CLS; F=Daily alerts, weekly remote follow-ups and quarterly patient-initiated interrogations; G=MV+ACC; H=80 minutes per year + 1 hour at implant; J=Accelerometer based rate response has negligible impact on battery at base rate (60 ppm); K=Turning on Reactive ATP is not anticipated to appreciably alter calculated longevity if therapy is successful at terminating the arrhythmia when applied. Longevity maybe impacted if continuous application of ATP is delivered and is unsuccessful at terminating the arrhythmia.; L=RF telemetry (remote monitoring and/or wireless communication): 1 hour at manufacture, 1 hour at implant, RF telemetry: 30 minutes/year; M= Values reflected assume a 27% or 3.2 months per year decline in estimated longevity associated with turning pre-EGM recording on for the lifetime of the device (in contrast to a 6 month period).

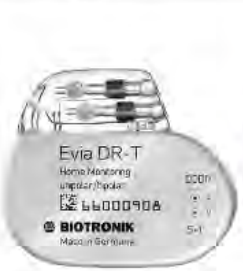
	Biotronik Evia	Boston Scientific Accolade EL	Boston Scientific Accolade	LivaNova Kora 100	Medtronic Advisa/Ensura™	St Jude Medical Assurity
						
Volume – DR/SR (cm^3)	12.0/11.0	15.8/NA	13.7/13.2	8.0/7.5	12.7/11.9	10.4/10.4
Useable Battery Capacity (Amp-hr)	1.2(DR)/ 1.05 (SR)[A]	1.6	1.0	0.81	1.10	0.91
Housekeeping current* (DR / SR; µA)	6.0/6.0	NA	NA	6.5/6.6	10.3/8.8	7.1/5.4
Battery chemistry, Manufacturer and identifier	QMR cell, Greatbatch 2596, Litronik Li-MnO_2, 3150	Li-CFx, Boston Scientific 402294	Li-CFx, Boston Scientific 402290	Li-Iodine Greatbatch 8711	Li-CFx+SVO Medtronic Delta 26H	QMR cell Greatbatch 2662
Features available						
RF communications	YES	YES	YES	NO	NO	YES
Home-monitoring	YES	YES	YES	YES[B]	YES[B]	YES
Sensor	CLS or ACC	MV + ACC	MV + ACC	MV + ACC	ACC	ACC
Programmable features off **						
Longevity (100% pace; DR / SR yrs)	9.5/13.4	12.7/NA	8.0/9.8	9.0/11.6[C]	8.7/11.7	NA/NA
Longevity (50% pace; DR / SR yrs)	12.0/>15	14.9/NA	9.3/10.7	11.3/13.4[C]	10.0/12.7	NA/NA
Programmable features on	HM[D], RR[E]	HM[F], Dual RR[G], RF[H]	HM[F], Dual RR[G], RF[H]	RM[B], Dual RR[G]	RM[B], RR[J], ATP[K], extended pre-arrhythmia IEGM	HM[L], RR[J], RF[L]
Longevity (100% pace; DR / SR yrs)	9.0/12.9	10.9/NA	7.2/8.7	8.0/10.1[C]	6.3/8.4[M]	9.1/13.5
Longevity (50% pace; DR / SR yrs)	11.5/14.5	12.4/NA	8.3/9.4	9.9/11.4[C]	7.2/9.1[M]	10.9/15.3
Shelf-life, months	6	6	6	6	5	6
Time from ERI to EOS, months	6	3	3	3	3	6.5/9.4

Figure 2: Predicted pacemaker longevity according to pacing load and advanced features. Single chamber pacemaker with (A) 50% pacing; (B) 100% pacing; Dual chamber pacemaker with (C) 50% pacing; (D) 100% pacing. Features on includes home monitoring and rate response for all manufacturers; radio frequency telemetry (Boston Scientific, LivaNova, and St Jude Medical); anti-tachycardia pacing and extended pre-arrhythmia IEGM (Medtronic). Note that St Jude Medical provides longevity estimates only with advanced features on.

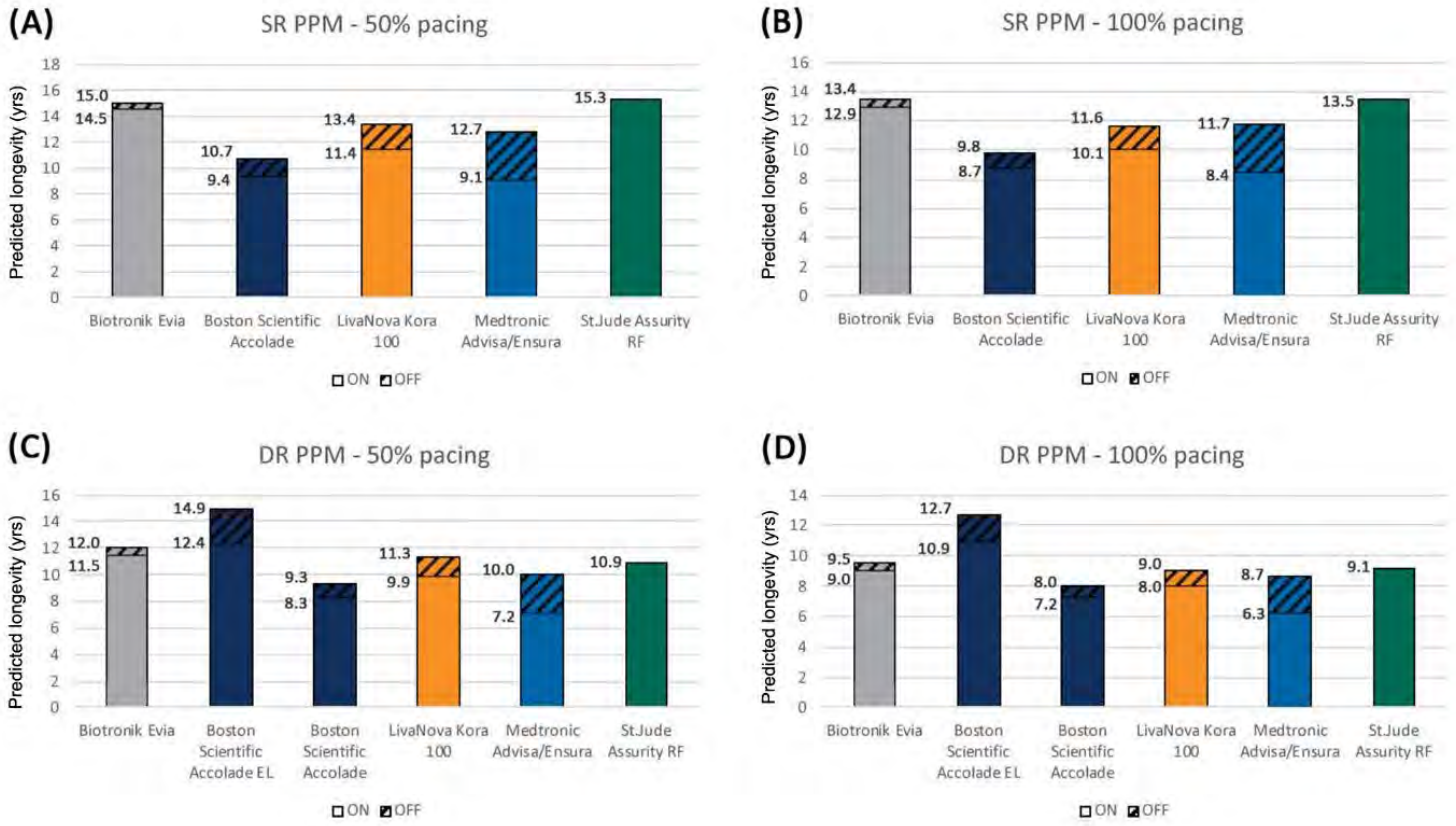


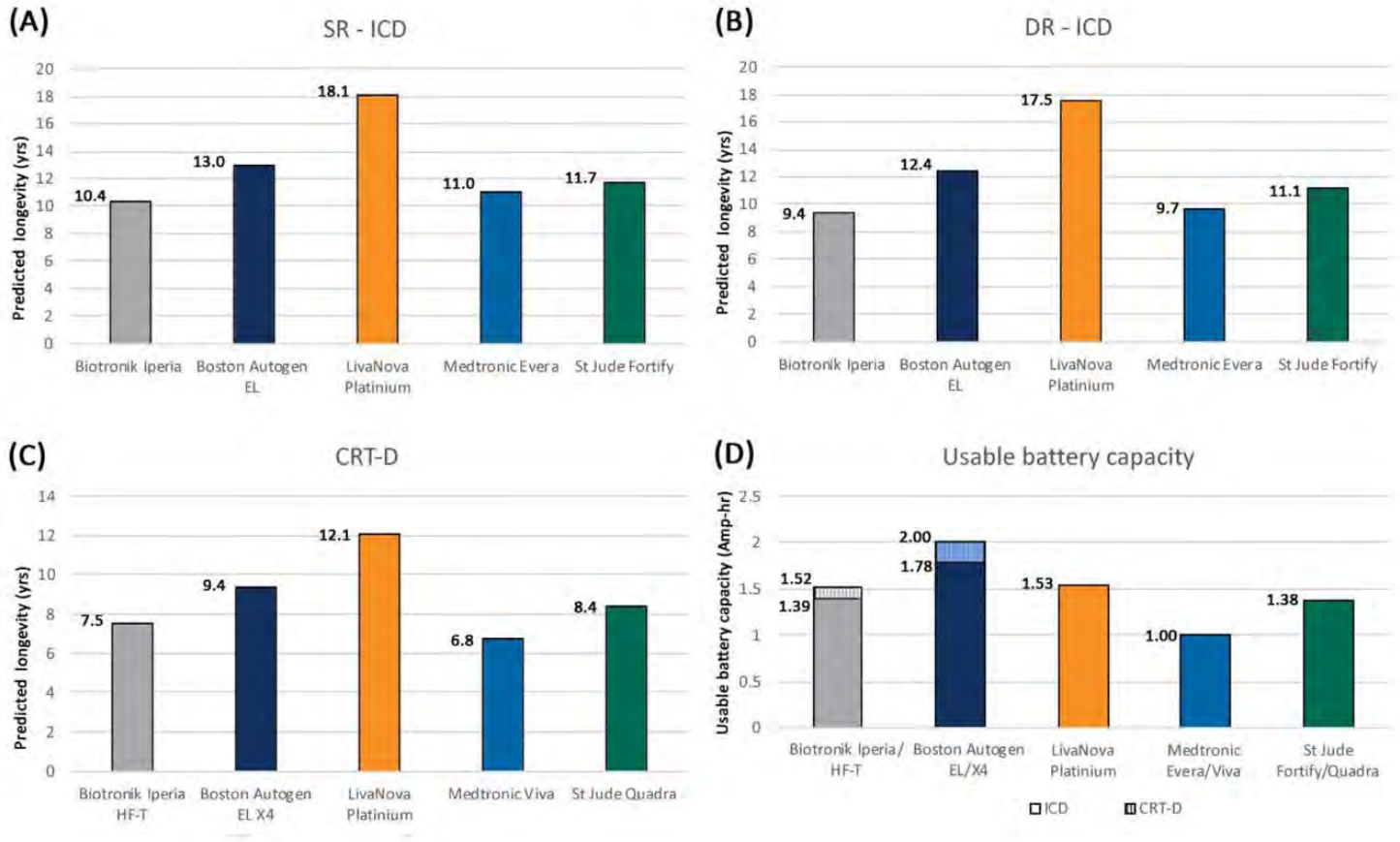
Figure 3: Physical characteristics, features and predicted longevities of ICD/CRT-Ds

All estimates are 2.5V; 0.40ms, 60 bpm, 500ohm lead. Ave=Average; Bi-V=Biventricular; bpm = beats per minute; DR=Dual chamber; ERI= Elective replacement indicator; EOS=End of Service; F/U=follow up; hr=hour; LV=Left ventricle; NA=not available; p.a.=per annum; PIT=Patient Initiated Transmission; RV=Right ventricle; RRT=recommended replacement time; SR=Single chamber; *=average back calculated housekeeping current from SR ICD, DR ICD and CRT-D; **=Zero clinical shock condition refers to only the number of full or partial energy charges required for capacitor and/or battery maintenance (except for Medtronic device, longevity calculation includes semi-annual maximum energy charging frequency and semi-annual battery form charging frequency [approximately equivalent to battery conditioning (4x18J) + 1 max charges]); ***="Usable battery capacity is 1.9 aH and residual usable capacity at explant is 0.12 aH for single chamber devices and 0.12 Ah for dual chamber devices."; A=Calculated longevity was estimated using a programmed pulse width of 0.35, which is equivalent to a delivered value of 0.366 ms.; B=The projected longevities with extended pre-IEGM recording for the entire life of the device (in contrast to a 6 month period) are in parentheses (actual values were reduced by 16, 20 and 24% for CRT, DR and VR devices, respectively); C=SonRTM (LivaNova) active; D=AdaptivCRTTM (Medtronic) (15% A, 100% LV, 50% RV); E=MultiPointTM (St Jude Medical) (15%A, 100% BiV MPP)

	Biotronik Iperia / Iperia HF-T	Boston Scientific Autogen EL/Autogen X4	LivaNova Platinium	Medtronic Evera/Viva®	St Jude Medical Fortify/Quadra Assura
					
Volume with DF-4 header, cm^3 (model)	31 [ICD] /36 [CRT]	29.5 (D174)	31.2 (1240)	33 (DVBB1D4)	35 (CD1261/2261-40Q) /38 (CD3271-40Q)
Total Battery Capacity, Amp-hr	1.520 [ICD] / 1,730 [CRT] (total) 1.390 [ICD] / 1.520 [CRT] (to RRT)	2.000 [ICD] /2.100 [CRT] (total)*** 1.780 [ICD] / 1.750 [CRT] (to RRT)	2.192 (total) 1.530 (to RRT)	N/A (total) 1.000 (to RRT)	1.944 (total) 1.377 (to RRT)
Battery chemistry Manufacturer and identifier	Hybrid Li-Cfx/Li-SVO (Greatbatch 2992) & Lithium/MnO2 (Litronik 3410 RA)	Lithium/MnO2 (Boston Scientific 401988)	Hybrid Li-CFx/Li-SVO (Quasar High Rate Greatbatch 3070)	Li-CFx/Li-SVO Medtronic 9455899	Hybrid Li-CFx/Li-SVO (Quasar High Rate Greatbatch 2850)
Ave back calculated housekeeping current (μA)*	18.4	18.3	11.4	13.0	15.4
RF communications	Not calculated	1 hr (3 hrs [CRT]) at implant 40 mins p.a.	1.5 hr at implant 60 mins p.a.	3 hrs at implant 60 mins p.a.	2 hrs at implant 60 mins p.a.
Home-monitoring	Daily check 12 F/U p.a.	Daily check 12 F/U p.a. 4 PIT	Daily check 4 F/U p.a. 5 full alerts p.a.	4 F/U p.a.	Daily check 4 F/U p.a. 5 full alerts p.a.
Sensor/accelerometer	OFF	OFF	OFF	OFF	ON
Maintenance capacitor/battery charges p.a.	4 x 40J	2 x 41J	2 X 34J	4 X 18 J	3
Longevity reduction with each additional shock	NA	~16 days (CRT) ~21 days (DR) ~21 days (VR)	NA	~ 24 days (CRT) ~ 33 days (DR) ~ 47 days (VR)	27 days
Shelf-life, months	6	6	6	5	6
Longevity with zero clinical shocks, years**					
0% pace; DR/SR	9.4/10.4	12.4/13.0	17.5/18.1	9.7[(7.8) B]/11.0 [(8.4) B]	11/11.7
15% pace; DR/SR	9.0/10.1	11.9/12.7	16.5[A]/17.5[A]	9.1[(7.5) B]/10.7 [(8.1) B]	10.5/11.4
15% A; 100% Bi-V	7.5	9.4	12.1[A]	6.8[(5.8) B]	8.4
Auto-BiV optimization	NA	NA	11.0[A, C]	7.3[D (6.1) B]	7.2[E]
Minimum time ERI TO EOS (months)	3 months 6x full charges VVI 50; 6V; 1.5 ms	3 months 3x 41J charges 100% VVI/DDD at 60/70 bpm, 2.5V A, RV, LV 0.4ms, 500ohm	11 months 11x 34J charges 100% DDD at 60 bpm, 3.5V A, RV, LV 500ohm	3 months 6x full charges 100% DDD at 60 bpm; 2.5V A and RV; 3V LV; 600ohm	4.9-5.4 months 6x 36J cdelivered 100% VVI at 60 bpm 2.5V RV 0.5ms 500ohm

Figure 4: Predicted ICD/CRT-D longevities and battery capacity

(A) Single chamber ICD devices with 0% pacing and zero clinical shocks; (B) Dual chamber ICD devices with 0% pacing and zero clinical shocks; (C) Biventricular ICD devices with 15% A pacing, 100% biventricular pacing, and zero clinical shocks.



CHAPTER 3

Complications related to Cardiac Implantable Electronic Device Implants: A Multivariate Survival Analysis of 3,832 Patients

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3.1.Introduction

Cardiac implantable electronic devices (CIEDs) have been proven to improve mortality and quality of life in patients with cardiovascular diseases.[164-167] As a result, the number of CIED implants is increasing worldwide. A report from Europe demonstrated that almost 750,000 new CIEDs were implanted in the year 2016, with the use of permanent pacemaker (PPM, implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy (CRT) increasing by 20%, 44%, and 121% respectively over the last 10 years.[168]

Although CIED procedures are considered relatively routine and low risk, there is still a risk of experiencing a complication during and after device implantation.[169] Recently a study using administrative coding based data from a Nationwide cohort of 81,304 patients undergoing new CIED implantation, has suggested that the rate of major complications was a staggering 8.2%, with higher incidence for ICDs than PPMs (10.04% vs 7.76%, respectively).[170] There are several potential reasons why there may be a high incidence of significant complications. As the complexity of devices increases there is often a requirement for the insertion of multiple leads rather than the single right ventricular lead used with early pacing systems. Increasing patient longevity results in many patients requiring repeat procedures to replace the CIED generator or other system components. These factors have the potential to result in higher complications rates, which are subsequently associated with increased morbidity and prolonged hospitalisation.[57]

Using a prospectively collected real world registry of CIED implants with patient level data, we sought to (1) determine the incidence of complication within the first 30 days after CIED implantation; and (2) to identify the predictors of complications following CIED implant.

3.2.Methods

3.2.1. Patient Population

The Genesis Cardiovascular Registry (GCOR) is a prospective multicentre observational registry established in the 14 Australian private hospitals setting designed to evaluate the outcomes of patients with standard indication of CIEDs procedure (table 1). All centres perform PPM, ICD, and CRT procedures, including new implants, generator replacements, system upgrades/downgrades, or revisions. All patients who underwent a CIED procedure were included. Between September 2015 and June 2018, the registry prospectively enrolled 4,757 consecutive patients at 14 hospitals in Australia. One unique feature of this registry is that all operators had a prior implant experience more than 500 cases. This factor would mitigate the effect of the learning curve seen in many other multicentre registries and may allow a true estimate of complication rates for established operators.

Each centre received written Human Research Ethics Committee (HREC) approval for collection of patient data and follow-up prior to participation (Bellberry HREC Eastwood, S.A.). The current study protocol was approved by HREC of the University of Adelaide, Adelaide, Australia.

3.2.2. Study protocol and data collection and management

Preprocedural patient characteristics that were collected included age, gender, cardiac diagnosis, previous surgery or cardiac intervention, medication, and cardiovascular risk factors. The technical details of implantation procedure such as type of devices, procedure time, leads, and prophylaxis antibiotics were also recorded. Evaluation of outcomes was performed in hospital, at 30 days, 1 year and 2 years post implant by telephone communication, office visit, or by contacts with primary physicians or referring cardiologists. A research nurse at each

hospital performed a standardised follow-up. At each evaluation, a determination was also made for medication regimen. The data was collected electronically at each participating medical centre. The registry is coordinated by a steering committee of cardiologists in collaboration with the Centre for Clinical Research Excellence in Therapeutics (CCRET, Monash University, Commercial Road, Prahran). CCRET meets standards relating to the use of paperless records under the Good Clinical Practice regulations and complies with the National E-Health Transition Authority (NEHTA) standard of reporting and storing data. The systems and processes with respect to privacy and data protection comply with relevant Health Records and Information Privacy Acts and Information Privacy Principles. Details of the registry have been previously presented.[171]

3.2.3. Study outcomes

The end-points of this study were: (1) Short term complication, defined as all complications occurred in-hospital and within 30 days after procedure; and (2) long-term complication, defined as all major complications occurred during the follow-up period. Complications were categorized into major and minor complications. Definitions of major and minor complication are described in table 2.

3.2.4. Predictors

Patient- and procedure-related variables included gender, age, centre volume, CIED type, procedure type, procedure time, and lead access. Age was divided into three groups: ≤59 years, 60–79 years, and ≥80 years. Centre volume was categorized according to procedure number during the study period per year: <20, 20-150, >150 procedures per year. CIED type was categorized as a single-chamber PM, dual-chamber PM, CRT-P, single-chamber ICD, dual-chamber ICD, and CRT-D. Procedure type consisted of three groups: new implant, generator

replacement, and surgical change of pacing mode (system upgrade), or lead revision. Procedure time was defined as the time from local anaesthetic infiltration to skin suture, and was categorised according to: <30, 30-60, and >60 minutes. Lead access was categorised as cephalic, axillary, or subclavian approach.

3.2.5. Statistical Analysis

Standard statistics were used to describe the baseline clinical characteristics, and procedural and clinical outcomes. Continuous variables are presented as mean ± SD or median (interquartile range [IQR]), as appropriate. Discrete variables are presented as counts and percentages and were compared by chi-square or Fisher exact test.

The incidence of short- and long-term complications was analysed, and time to any major complication was estimated using the Kaplan-Meier method. The prognostic relevance of the on the occurrence of major complications was assessed with Cox proportional hazards regression models. Proportional hazard assumption (PHA) analysis was analysed, showing the criteria is met for procedure time variable. In multivariate analyses, we included variables that were considered significant and a priori selected potential confounders. A sub-group analysis was performed to estimate the incidence of infection related to CIED type (PM/CRT-P vs. ICD/CRT-D), procedure type (de novo/replacement/upgrade/revision), and the use of anti-platelet or anticoagulation. A P-value (two-sided) of 0.05 was considered statistically significant. SPSS software (SPSS for Windows, version 25) was used for statistical analyses.

3.3.Results

3.3.1. Study population

During the study period, a total of 4,641 patients underwent CIED procedure. Patients with non-transvenous devices (ILR=771, leadless PM=6, subcutaneous ICD=7) were excluded. 25 patients were also excluded due to loss to follow-up. As a result, a total of 3,832 patients with transvenous CIEDs (pacemakers: SR=574; DR=2,229; biventricular=193; and defibrillators: SR=160; DR=327; biventricular=349) were included in the analysis and followed for a median of 335 (interquartile range (IQR) 32-381) days, resulting in a total of 2,477 patient-years. The details of patient and procedure characteristics are shown in table 3. Median age at implantation was 77.2 (IQR 69.7-83.8), and 38.2% (n=1,464) of patients were women.

3.3.2. Patient and procedural characteristics

Majority of procedures were de novo CIED implant (2,871 patients – 72.6%). Meanwhile, the proportion of replacements, upgrades, and revisions were 22.3%, 4.3%, and 0.7%, respectively. Figure 1 shows the detail of study enrolment chart. No significant differences were found in the age, gender, and cardiac history between the group of patients with and without complication (table 3).

3.3.3. Incidence of short-term complications

Overall, 80 patients (2.1%) and 85 patients (2.4%) experienced at least one major complication before discharged and at 30 days of follow-up, respectively, resulting in the cumulative incidence of 4.3% within the first 30 days period (Table 4). Lead dislodgement requiring intervention was the most common complication occurring either detected prehospital discharge or in the first 30 day follow up period, at 0.7% and 0.8%, respectively, with a total of 1.3% of patients. A total of 32 patients (0.9%) died within 30 days of procedure. The detail

of cause of death is described in table 5. In-hospital and 30 days minor complication occurred in 1.4% and 5.2% of patients, respectively.

An additional sub-analysis was performed to evaluate early major complication based on type of procedure (figure 2). This analysis revealed a tendency of higher incidence of infection in replacement and upgrade procedure as compared to new implant, at 0.93% and 1.2% vs 0.47%, respectively (p value 0.052, odd ratio (OR) 1.83, 95% confidence interval (CI) 0.99-3.38). Additionally, a similar pattern was also found in the incidence of major bleeding or hematoma with prolonged hospitalisation, at 0.35% and 0.6% vs 0.22%, respectively (p value 0.28, OR 1.66, 95% CI 0.65-4.20).

3.3.4. Sub-analysis on short-term infection

Table 6 demonstrated the sub-analysis of procedure characteristics that may be related to 30-days outcome of infection. No significant statistical different were found based on vein approach, pocket irrigation with antibiotics, antibiotic premedication, type of implanted device, or types of procedures. However, there was a trend towards infection occurrence in patients with wound closure using skin glue compared to suture with a rate of 1.5% and 0.5%, respectively (p value 0.051, OR 3.01, 95% CI 0.99-9.14).

3.3.5. Long term complication

Within 2-year follow-up period, there were 203 major complications reported that occurred in 199 patients (cumulative incidence of 5.2%). The survival analysis of freedom from any major complication shown in figure 3A demonstrated a steep slope in the first 30 days after the procedure, followed by a more gradual decline, which indicates a higher incidence of major

complications early after implantation. The incidence of major complication gradually declined during 1- and 2-years follow-up, at 1.4% and 1.2%, respectively.

3.3.6. Predictors

Patient and procedure characteristic variable for long-term major complications was analysed in multivariable analysis (figure 4). This analysis demonstrated that procedure time >30 minutes is significantly associated with almost three times higher incidence of major complication (Hazard ratio (HR) 2.90; 95% CI 1.87-4.53; p value <0.001). In multivariate analysis, it is shown that procedure time >30 minutes is an independent predictor of major complication (HR 2.22 (95% CI 1.32-3.74, p 0.002) (figure 3B). Notably, centre volume showed no independent predictive effect on the occurrence of complications (HR 0.72 (95% CI 0.21-2.51), p value 0.6 and HR 0.64 (95% CI 0.20-2.04), p value 0.5; for centre volume of 50-150 and >150 per year, respectively, as compared to low volume centre (<50 per year)).

3.4.Discussions

3.4.1. Major Findings

This study is a prospective, multicentre, real-world registry of complications related to pacemaker, ICD, and CRT implantation procedures. Specifically, several important findings from our study are as follows:

- A low rate of short-term complication (30-days) after CIED implantation were notable at 4.3% of cases.
- 30-days infection rate was 0.6%, with an increasing trend towards the procedures using skin glue as wound closure approach as compared to suture (1.4% vs 0.5%, respectively).

- The incidence of long-term complication was gradually decreased at 1 and 2 years (1.4% and 1.2%, respectively)
- Procedure time>30 minutes is an independent predictor of complication after CIED implantation procedures

To our knowledge, this registry is the largest reported data collected prospectively with patient level data to evaluate all complications related to CIED procedure. The prospective nature of our data collection and the intensive follow-up after the procedure which allows this data more robust in representing the real incidence of complications in CIED related procedures in comparison to an administrative dataset.

3.4.2. Discrepancies between administrative datasets and medical record-based registry

This study highlights the limitations of prior studies that have used administrative datasets without the availability of prospective data collection with patient level information, which reported a higher incidence of CIED related complication.[170] Whilst such data have advantages of being widely available with lower cost and effort as compared to medical record review, differences of disease estimates or complication rates from administrative data and medical record based registry have been reported previously for various medical conditions. In all instances, administrative data estimates are significantly higher.[172-174] Reason for these discrepancies were mainly influenced by the quality of reporting and coding issues, including coding errors. Previous reports showed high likelihood of false positive cases when validating diagnosis based on ICD codes compared to medical records with various positive predictive value, ranging from 55% to 90%, depending on the coding methods.[172,174] In addition, the impact of medical coding and billing linkage may potentially cause “over coding” phenomenon in order to increase hospital revenue, which further affect the number of false positive coding based diagnosis.

3.4.3. Risks of complications

Despite continuous evolution of technique and technology in CIED procedures, complications may still frequently occur. Most studies report 5-10% risk of any complication related to CIED procedures,[57,169] although the difference in the complication definition or varying follow-up period could interfere the comparison of complication incidence.

In this study, there was a 0.6% or mortality rate within 30 days of procedure. This rate is much lower than previous report from Denmark cohort which demonstrated a mortality of 5.5% in the first six months after procedure.[57] Nevertheless, we observed that this event is more often related to the severity of the disease itself rather than to the procedure. In our study, a higher mortality rate was found in patients who either were octogenarian (68.8%), had a background of AF (70%) or HF (40%).

In the *de novo* CIED implantation, we found that infection rate was the lowest at 0.5% compared to replacements or upgrades. This finding is in line with other reported studies with around 1% infection rate.[175,176] Post-operative hematoma have been postulated to be one of the main factors. Essebag et al, in the Bruise Control Infection study (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial Extended Follow-Up for Infection) study, found that hematoma increased 7.7-fold of infection risk, with mechanisms including compressive effects of a blood clot leading to necrotic tissue in the suture line, contamination caused by wound tension, microorganism colonization because of a fertile environment result in the delay of wound healing delay.[177] However, our study is not powered to assess this correlation, therefore this unfortunately could not be shown in our study.

This present study also identified a very low rate of infection for generator replacements and upgrades (0.9% and 1.2%, respectively). These rates were lower than those of major complications reported in the REPLACE Registry in 2010, which ranged from 4.0% to 15.3% in patients undergoing generator exchange and upgrade procedures, respectively. This seems to be affected by the introduction of antibacterial envelope to reduce CIED infections since 2008 that showed a promising results.[178] In the earlier studies of general CIED implantations, the use of antibacterial envelopes demonstrated a low CIED infection rate, ranging between 0.4%-1.1%.[179-181] A subsequent investigation in ICD and CRT-D replacements also showed similar result with CIED infection rate of 0.7%, which is comparable with our study.

3.4.4. Predictors

A recent published meta-analysis has proved that there was a robust association of long duration of surgery with procedure-related complication, even in general surgery population, across surgical specialties.[182] Particularly in CIED procedures, Ebehardt et al also demonstrated that prolonged operation time led to a higher complication rate, although it was only noticeable among the operator with less experience.[183] In accordance to the previous results, we found that a two-times greater complication risk in CIED with prolonged procedure duration with cutoff value of 30 minutes.

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Despite the factors that complication may occur at random, several other factors related to complication incidence have been described. For patient characteristics, Herce at al showed that the presence of diabetes and underlying heart disease are related to three times higher incidence of infection after cardiac device implantation.[184] Aging of the population as well as increasing number of comorbidities and prescription of anticoagulants and antiplatelet agents may also be related to higher complication rate.[185,186] In addition, device characteristics

including type of devices with a larger number of leads also influence the procedure outcomes.[57,184] As regards procedural characteristics, the experience of the hospital and the surgical team performing the procedure are strongly associated with the number of complications.[187,188] Furthermore, early re-intervention are also associated with a higher infection rate. [184]

3.4.5. Limitations of the study

This study presents some limitation that must be considered in interpreting the results. By design, this is a registry-based cohort study from multicentre which is prone to underreported outcomes, especially if the patients did not attend their appointment. However, this pitfall has been addressed with regular evaluation by telephone communication or by contacts with primary physicians or referring cardiologists. In addition, this registry was not designed to evaluate the relationship between individual patient risk factors and subsequent complications. Therefore, some baseline characteristics are not available in the registry.

3.5.Conclusions

This prospective cohort showed that the incidence of 30 days complications after CIEDs implant was low when undertaken by experienced operators. Procedure duration seems to be strongly related to the incidence of complications.

3.6.Tables

Table 1. Participating Centres

State	Hospital Name	Number of cases – n (%)
Queensland	Wesley Hospital	824 (21.5)
	Greenslopes Hospital	150 (3.9)
	Mater Hospital	112 (2.9)
	Friendly Society Hospital	401 (10.5)
Victoria	Warringal Hospital	432 (11.3)
	Valley Hospital	279 (7.3)
	Epworth Richmond Hospital	4 (0.1)
	Epworth Eastern Hospital	70 (1.9)
South Australia	Wakefield Hospital	18 (0.5)
	St Andrews Hospital	535 (14.0)
Western Australia	Mount Hospital	466 (12.2)
	St John Of God Murdoch	446 (11.6)
	Joondalup Health Campus	22 (0.6)
	Bunbury SJOG Hospital	73 (1.9)

Table 2. Definition of complications

Major complications	- death of any cause within 30 days of the procedure; - respiratory arrest/failure within 24 h of the procedure requiring ventilator support or intubation; - acute coronary syndrome directly related to the procedure; - cardiac perforation requiring pericardiocentesis or other surgical intervention; - pneumothorax requiring observation or chest tube placement; - stroke within 30 days of the procedure; - infection requiring intravenous antibiotics and or system removal/extraction; - generator or lead malfunction requiring reoperation; pocket revision requiring reoperation; - major bleeding or hematoma requiring evacuation, drainage, blood transfusion, hospitalization, or extension of hospital stay to treat hematoma; - hospital readmission directly related to the generator replacement procedure; - coronary venous dissection with hemodynamic instability; - pulmonary embolism; - peripheral arterial embolism; - deep vein thrombosis; - drug reaction resulting in an aborted procedure; - cardiac valve injury or AV fistula related to the replacement procedure.
Minor complications	- hematoma lasting more than 7 days with tenseness, drainage, or minor dehiscence managed as an outpatient; - hematomas without tenseness but requiring additional outpatient evaluation; - implant related pain lasting more than 7 days requiring prolonged use of narcotic pain medications; - cellulitis treated as an outpatient with oral antibiotics; - minor surgical wound findings; - peripheral nerve injury; - superficial phlebitis

Table 3. Patient and procedure characteristics (n=3,832)

Variables	n	%
Age		
- <59	311	8.1
- 60-79	2,033	53.1
- >80	1,488	38.8
Gender (n, %)		
- female	1,464	38.2
- male	2,367	61.8
Cardiac history:		
- Atrial Fibrillation	1,937	53.6
- Myocardial infarction	555	15.9
- Heart Failure	970	27.8
- Percutaneous intervention	551	15.6
- Coronary Artery Bypass surgery	504	14.3
- Valvular surgery	377	10.7
Type of procedures (n, %)		
- De novo	2,771	72.5
- Replacement	854	22.4
- Upgrade	164	4.3
- Revision	27	0.7
Type of devices (n, %)		
- Pacemaker – SR	579	15.0
- Pacemaker – DR	2,241	58.1
- ICD – SR	161	4.2
- ICD – DR	331	8.6
- CRT – P	195	5.1
- CRT – D	350	9.1
Indication of implantation:		
- Pacemakers (n=2,791)		73.1
- Sinus node dysfunction	1,572	
- AV Block	973	
- Trifascicular block with syncope	73	
- Others	57	
- Unknown	116	
- ICDs (n=486)		12.8
- Primary prevention	306	
- Secondary prevention	143	
- Others	37	
- CRT/Ds (n=539)		14.1
- Primary prevention	115	
- Secondary prevention	30	
- Heart failure for resynchronization	188	
- Resynchronization with AICD	158	
- Pacing with LV dysfunction	4	
- Unknown	44	

Table 3. Patient and procedure characteristics (cont.)

Variables	n	%
Lead access		
- Cephalic	206	7.6
- Axillary	761	28.2
- Subclavian	1,730	64.1
Lead position		
- Atrial leads (n=2,246)		
- High right atrium	3	0.1
- Atrial appendage	1,893	84.3
- Others	37	1.7
- Unknown	313	13.9
- Right ventricular leads		
- Apex	1,160	39.4
- Outflow tract	434	14.8
- His bundle	16	0.5
- Mid septum	822	28.0
- Others	71	2.4
- Unknown	438	14.9
Procedure time		
- <30 minutes	1,037	41.0
- 30-60 minutes	1,493	59.0
Centre volume		
- <50 per year	187	4.9
- 50-150 per year	541	14.1
- >150 per year	3104	81.0
Medications		
- Antiplatelet	989	25.8
- Anticoagulation		
• Warfarin	389	10.1
• DOAC	956	25.0

Table 4. Incidence of major and minor complication at in-hospital, 30 days, 1 year, and 2 years after implantation

	In-hospital N=3,832	**30 days N=3,500**	**1 year N=2,167**	**2 years N=377**
	No. of events (%)	**No. of events (%)**	**No. of events (%)**	**No. of events (%)**
Major complication	**80 (2.1)**	**85 (2.4%)**	**30 (1.4%)**	**5 (1.2%)**
- Death within 30 days	10 (0.3)	22 (0.6)	NR	NR
- Cardiac perforation requiring intervention	2 (0.05)	2 (0.06)	NR	NR
- Pneumothorax	22 (0.6)	5 (0.1)	NR	NR
- Generator/lead malfunction	1 (0.03)	0 (0)	6 (0.3)	1 (0.3)
- Lead dislodgement requiring intervention	27 (0.7)	27 (1.8)	7 (0.3)	1 (0.3)
- Infection	3 (0.08)	20 (0.6)	5 (0.2)	1 (0.3)
- Pocket revision	1 (0.03)	0 (0.03)	1 (0.05)	0
- Major bleeding or hematoma with prolonged hospitalisation	9 (0.23)	1 (0.03)	1 (0.05)	0
- Deep vein thrombosis	0 (0)	6 (0.2)	1 (0.05)	1 (0.3)
- Stroke	2 (0.05)	2 (0.06)	9 (0.41)	1 (0.3)
- Acute coronary syndrome	1 (0.03)	NR	NR	NR
- Respiratory failure in 24 hours	2 (0.05)	NR	NR	NR
- Anaphylactic shock	1 (0.03)	NR	NR	NR
- Acute heart failure	2 (0.05)	NR	NR	NR
Minor complication	**53 (1.4)**	**157 (4.5)**	**61 (2.8)**	**2 (0.5)**
- Bleeding and hematoma not requiring intervention	25 (0.6)	39 (1.8)	NR	NR
- Lead dislodgement not requiring intervention	1 (0.03)	6 (0.2)	4 (0.2)	2 (0.5)
- Vascular trauma	2 (0.05)	0 (0)	NR	NR
- Acute kidney injury - resolved	3 (0.1)	5 (0.2)	6 (0.3)	NR
- Pericardial effusion not requiring intervention	14 (0.4)	12 (0.7)	2 (0.1)	NR
- Phrenic nerve stimulation	3 (0.1)	8 (0.3)	1 (0.05)	0
- Surgical emphysema	1 (0.03)	0 (0)	NR	NR
- Arrhythmia requiring intervention	2 (0.05)	85 (2.5)	48 (2.2)	NR
- Prolonged pain at pocket site	1 (0.03)	0 (0)	NR	NR
- Pericarditis	1 (0.03)	1 (0.06)	NR	NR
- Thrombophlebitis	0 (0)	1 (0.03)	NR	NR

NR=Not relevant

Table 5. Cause of 30 days mortality (n=32 patients)

Cause of Death	N (%)
1. Cardiovascular cause (including sudden death, MI, unstable angina or other coronary artery disease, heart failure or arrhythmia	4 (12.5%)
2. Infection (including sepsis, pneumonia)	2 (6.2%)
3. Multi organ failure	1 (3.8%)
4. Death related to device complication	4 (12.5%)
5. Unknown	21

Table 6. Procedure characteristics related to infections

	Infection (-)	Infection (+)	P Value
Venous access			0.188
Cephalic	205 (99.5%)	1 (0.5%)	
Axillary	760 (99.1%)	7 (0.9%)	
Subclavian	1,732 (99.7%)	6 (0.3%)	
Wound closure			0.114
Skin glues	204 (98.6%)	3 (1.4%)	
Suture	3,061 (99.5%)	16 (0.5%)	
Pocket irrigation			0.959
No irrigation	2,274 (99.4%)	13 (0.6%)	
Antibiotic irrigation	239 (99.6%)	1 (0.4%)	
Betadine irrigation	3 (100%)	0 (0)	
Antibiotic envelope	25 (100%)	0 (0)	
Prophylactic antibiotics			0.001
Antibiotic IV	2,483 (99.5%)	13 (0.5%)	
Antibiotic oral	37 (94.9%)	2 (5.1%)	
No antibiotics	1,206 (99.3%)	8 (0.7%)	
Types of devices			0.454
PPM-SR	576 (99.5%)	3 (0.5%)	
PPM-DR	2,228 (99.4%)	13 (0.6%)	
CRT-P	195 (100%)	0 (0)	
ICD-SR	161 (100%)	0 (0)	
ICD-DR	327 (98.8%)	4 (1.2%)	
CRT-D	347 (99.1%)	3 (0.9%)	
Types of procedures			0.311
New	2,773 (99.5%)	13 (0.5%)	
Replacement	854 (99.1%)	8 (0.9%)	
Upgrade	164 (98.8%)	2 (1.2%)	
Revision	27 (100%)	0 (0)	
Oral anticoagulation			0.585
No medication	2,481	14 (0.6%)	
DOAC	962	7 (0.7%)	
Warfarin	388	1 (0.3%)	

3.7.Figures

Figure 1. Study enrolment flowchart. CRTP/D=Cardiac resynchronization therapy pacemaker/defibrillator; ICD=Implantable cardioverter defibrillator; PPM=Permanent pacemaker.

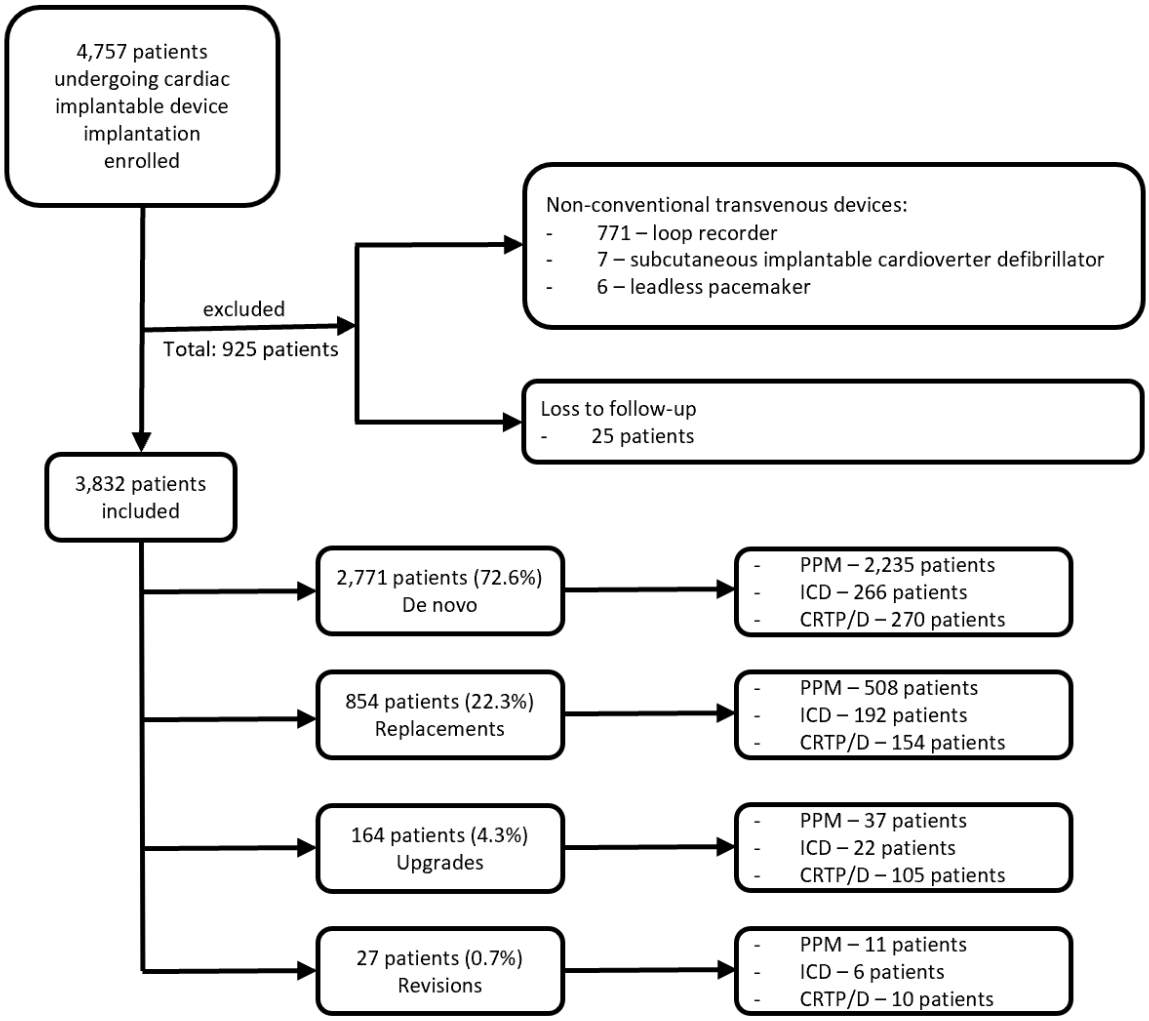


Figure 2. Incidence of short-term major complication based on type of procedure

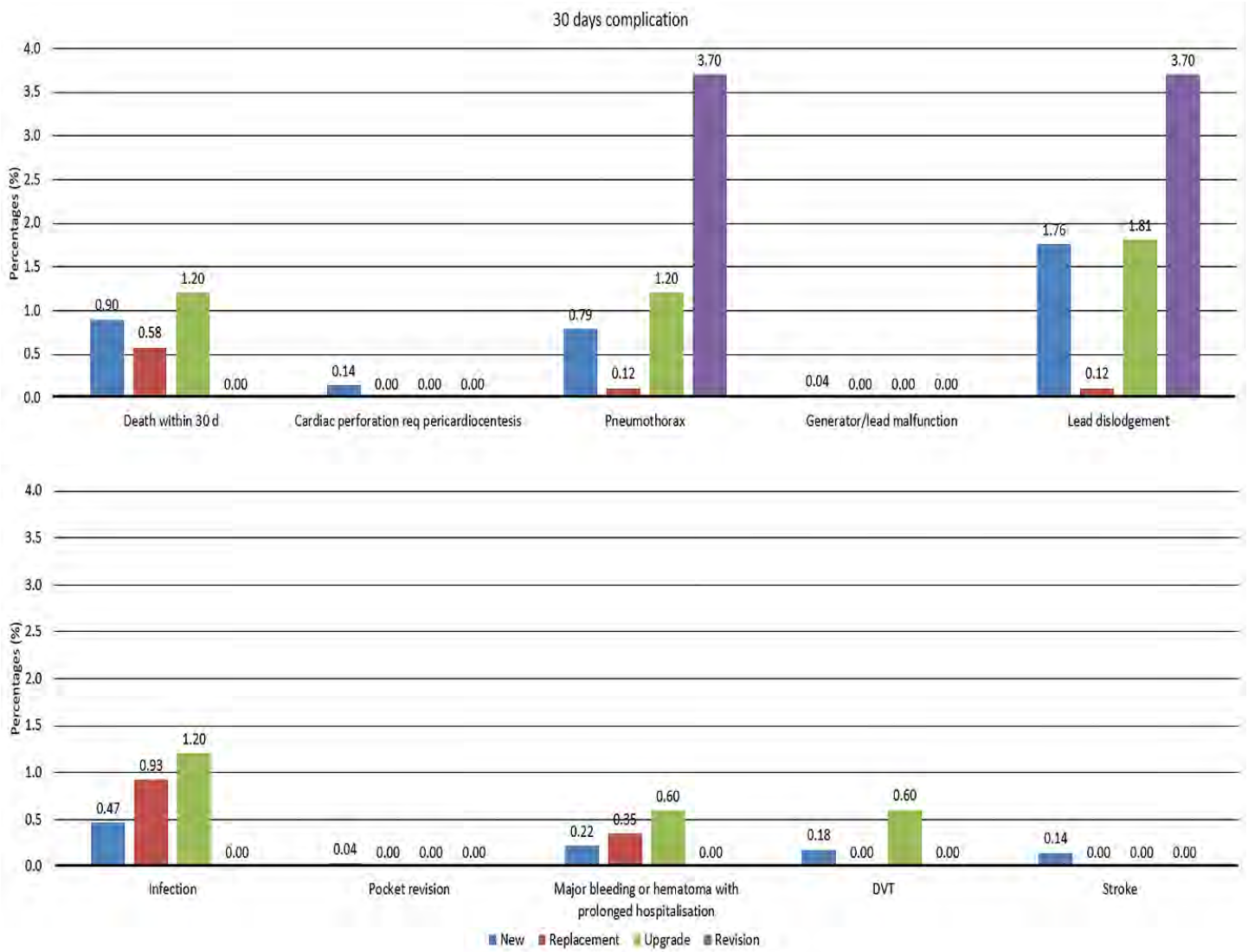


Figure 3. Kaplan-Meier curve of major complication (A) survival during a median follow up of 335 days (B) survival based on procedure time

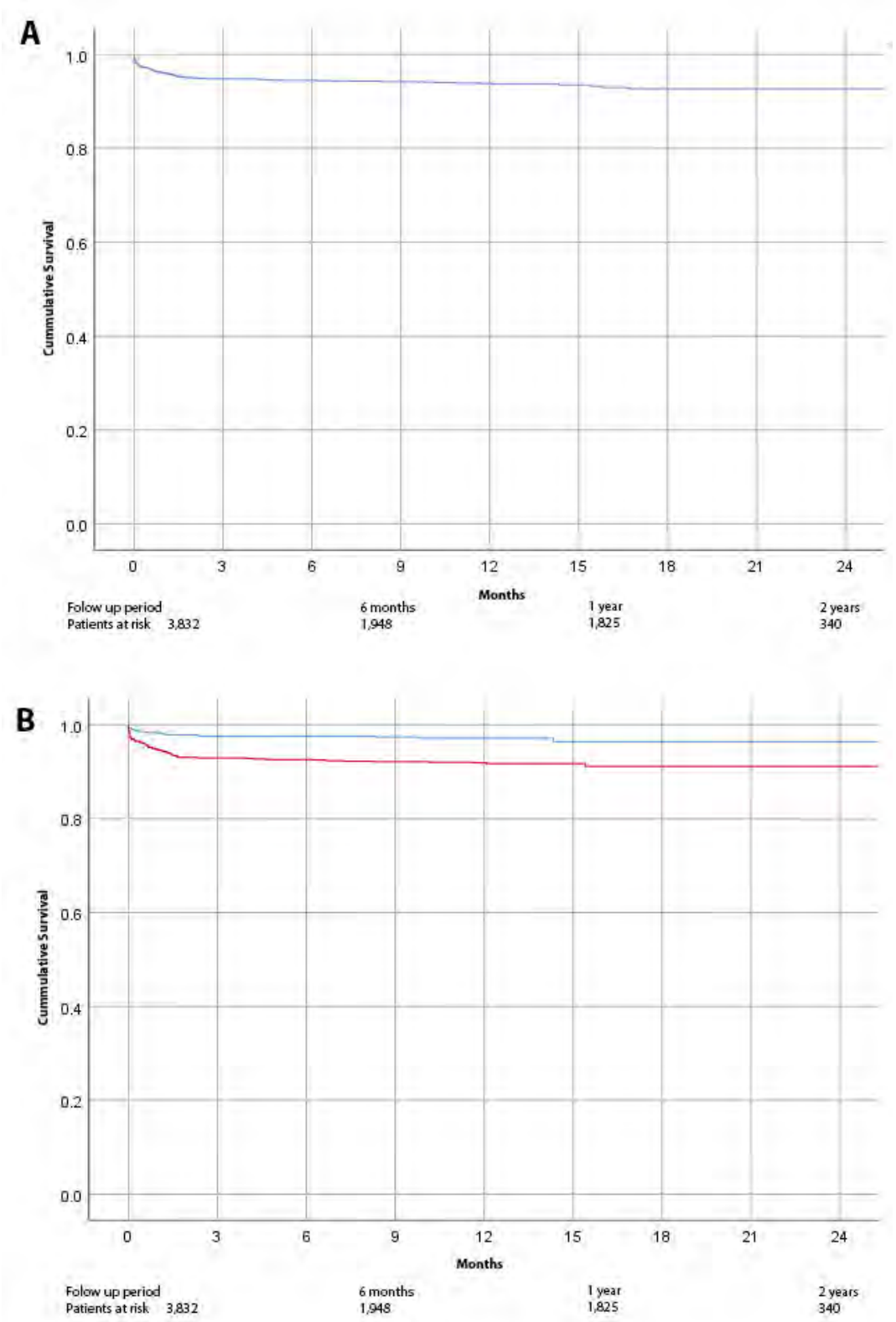
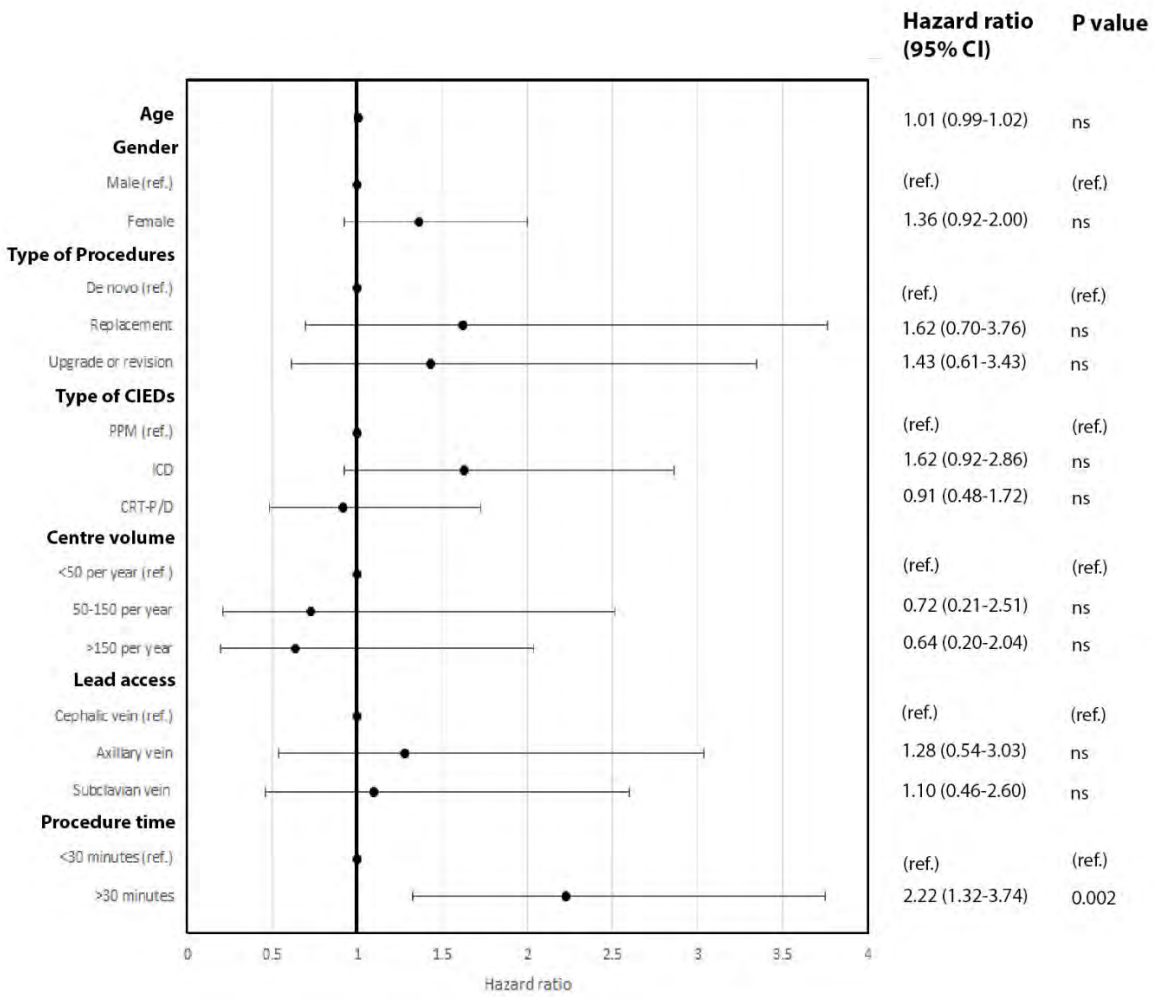


Figure 4. Adjusted hazard ratio of major complication



CHAPTER 4

Transvenous Cardiac Implantable Devices and Pulmonary Hypertension: An Echocardiographic Evaluation in a Cohort Study

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4.1.Introduction

Cardiovascular implantable electronic devices (CIED) have been implanted transvenously for nearly the last five decades. Although these devices have been demonstrated to be lifesaving with a good safety profile, these patients are at risk of developing venous complications. Venous abnormalities on venous angiograms or Doppler are seen in up to 23% of patients at 1 year after transvenous permanent pacemaker implantation.[81,189,190] Symptomatic venous thrombosis is less common and complicates only 0-6% of all pacemaker implants.[189,191-194] Possible contributing factors include foreign body reaction, endothelial trauma and lead-related venous flow obstruction and turbulence.[195] CIED related venous thrombosis can cause local morbidity such as swelling and pain and can also be a source of pulmonary embolism.[196,197] Although venous thrombosis may be easily recognized, intracardiac lead related thrombi may often be asymptomatic and remain under recognized.[77] An intracardiac echocardiography based study has demonstrated the high prevalence of intracardiac lead related thrombi, at around 30%.[77] Similarly, an autopsy based study has shown that 14% of patients with pacemakers had right atrial lead thrombosis at an average of 4 years post implantation.[78] Additionally, numerous case reports described that intracardiac lead thrombus is associated with pulmonary embolism (PE) and development of subsequent right heart failure.[198-201] Although symptomatic PE is uncommon, asymptomatic PE may occur. One study observed that ventilation-perfusion defects occurred in 15% of patients within 14 days of pacemaker implant.[202]

Although there are case reports demonstrating PM lead related thromboembolism[77,78,81,169,190,194,198,199,201], there is a paucity of data evaluating the development of PH following pacemaker implantation. We hypothesize the development of pulmonary hypertension (PH) secondary to subclinical pulmonary emboli. In view to this, we

examined the echocardiographic data from a prospectively collected registry of CIED patients to characterise the development of PH in patients with chronic transvenous devices.

4.2.Methods

4.2.1. Study population and design

This study was a single centre, observational cohort study. Data was obtained from an existing clinical database at the Centre for Heart Rhythm Disorders, University of Adelaide, Australia. All adult patients who underwent de novo transvenous CIED implantation from 2009 to 2017 were considered for inclusion. The following exclusion criteria was used: age less than 18 years of age; no echocardiographic evaluation at baseline (3 months prior up to 1 month of implant); no echocardiogram or clinical follow-up at least 6 months after device implant; documented severe elevated pulmonary pressure on baseline echocardiogram, or known congenital heart disease. The current study protocol was approved by HREC of the University of Adelaide, Adelaide, Australia.

4.2.2. Data collection

Case sheets, echocardiograms, and device interrogation report were collected from the day of implantation and during their clinical visits. The demographic characteristics of the study subjects recorded from medical records, including: 1) physical characteristics (age, sex, body mass index [BMI, kg/m-2]); 2) comorbidity-related information (hypertension, diabetes mellitus, hyperlipidemia, cardiomyopathy, stroke, obstructive sleep apnea (OSA), deep vein thrombosis (DVT)/pulmonary embolism (PE), coronary artery disease/myocardial infarction, alcohol intake, renal impairment); 3) device-related characteristics (type of devices, atrial pacing percentage, ventricular pacing percentage, arrhythmias burden); 4) history of arrhythmias (atrial fibrillation, atrial flutter, atrial tachycardia, ventricular tachycardia); 5)

history of catheter ablation, intervention, or cardiac surgery; 6) Antiplatelet and anticoagulation use; and 7) Other cardiac medications (angiotensin-converting-enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, beta blocker, anti-arrhythmic agent).

Evaluation of outcomes measured by echocardiogram was performed at baseline (ranging between 3 months prior until 1 month after implantation). The echocardiogram follow-up was performed at least 6 months after procedure, then every year to monitor any increase of right heart pressure. The detail of echocardiographic measurement is described below.

4.2.3. Echocardiographic evaluation

Echocardiographic assessment was undertaken according to the guidelines of right heart assessment in adults published by American Society of Echocardiography.[203,204] Systolic pulmonary artery pressure (SPAP) was estimated using the measurement of continuous wave Doppler of peak tricuspid regurgitation velocity (TRV), using the simplified Bernoulli equation and combining this value with an estimate of the RA pressure: $RVSP = 4(TRV)^2 + RA\ pressure$. TRV is the peak velocity (in meters per second) of the tricuspid valve regurgitant jet, measured by continuous wave Doppler signals acquired from the parasternal short axis, right ventricular inflow, and apical 4-chamber views. Only waveforms with well-defined "envelopes" were measured. RA pressure is estimated based on the diameter and respiratory variation in diameter of the inferior vena cava (IVC): an IVC diameter of 2.1 cm that collapses ≥50% with a sniff suggests a normal RA pressure of 3 mmHg (range 0–5 mmHg), whereas an IVC diameter of 2.1 cm that collapses ≤50% with a sniff or ≤20% on quiet inspiration suggests a high RA pressure of 15 mmHg (range 10–20 mmHg).[203] Classification of PH probability from an echocardiographic examination was derived from the 2015 ESC Guideline for diagnosis and treatment of pulmonary hypertension.[205] This guidelines suggests grading the probability of

PH based on TRV at rest and on the presence of additional pre-specified echocardiographic variables suggestive of PH (table 1).

In addition to the assessment of PH, routine echocardiographic parameter, such as 1) Left ventricular (LV) ejection fraction (measured in biplane); 2) LV end diastolic and end systolic volume (EDD and ESV); 3) Right and left atrial area; 4) Diastology measurement; and 5) Valvular abnormalities (including mitral stenosis/regurgitation, aortic stenosis/regurgitation, and tricuspid stenosis/regurgitation), were also collected.

Echocardiograms were acquired with a GE Vivid imaging platform and were stored in a digital format for subsequent analysis, using a protocol that included ≥3 cardiac cycles for each image. All echocardiographic measurements were made using off-line echocardiographic analysis software. Echocardiogram assessment was performed by certified cardiac physiologists specialised in echocardiography and validated by experienced cardiologists. Both examiners were blinded to the study protocol.

4.2.4. Study Outcomes

The primary outcome of this study is the incidence of pulmonary hypertension (PH) measured from echocardiogram that is classified as high PH probability, as described in the 2015 European Society Guidelines of Pulmonary Hypertension.[205,206] It is defined as peak TRV more than 3.4 m/s; or peak TRV of 2.8-3.4 m/s with at least two criteria of additional parameters described above on follow-up.

The secondary outcome of this study is the assessment of independent predictors from baseline characteristics, including clinical and echocardiogram variables, in relation to PH development.

4.2.5. Statistical analysis

Statistical analyses were performed using SPSS version 25 (IBM Inc, Armonk, NY, USA). Normally distributed continuous data will be expressed as mean ± standard deviation and tested with unpaired t-tests between groups. Skewed distributions will be expressed as median and inter-quartile and means tested using Mann-Whitney U. A Cox proportional-hazards analysis was performed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) In multivariate analyses, we included variables that were considered significant (p value <0.1 on univariate analysis) and a priori selected potential confounders. Proportional hazard assumption (PHA) analysis was met for all significant variables. Variables in the multivariable models represent the most common confounding or mediating factors of the association between CIED and the development of PH. Survival curves with 95% CIs and corresponding number at risk tables are presented. A p value < 0.05 was considered to be statistically significant.

4.3.Results

4.3.1. Patient Characteristics

Of all patients undergoing CIED implantation during the study period (N=1,572 patients), 440 patients were excluded (5 patients had cardiac congenital disease, 19 patients had documented PH at baseline, 142 patients with <6 months echocardiogram follow up, 75 patients with no echocardiogram at baseline, and 189 patients were lost to follow up). As a result, 1,132 participants were included in the analysis (figure 1).

Baseline characteristics of the study participants are listed in table 2 and 3. In general, the median age of study participants was 73.0 (interquartile range (IQR) 64.6-80.1) years and 38.6%

of participants are female. The highest proportion of implanted CIED type is pacemaker at 70.8% as compared to ICD (13.3%), CRT-P (2.7%), or CRT-D (5.4%). 405 patients (35.8%) were given oral anticoagulation for any reasons (including thromboembolic events, atrial fibrillation with high CHA_2DS_2-VASc score).

4.3.2. Primary outcomes

The primary outcome of this study is the development of significant pulmonary hypertension measured by echocardiogram as mentioned above. After a median follow-up of 45 (IQR 27-71) months, pulmonary hypertension occurred in 53 patients (4.7%). The development of pulmonary hypertension varied between 7 and 108 months after procedure. No difference in the follow-up period between PH vs non-PH group (49 (IQR 26-71) vs 45 (27-71) months, p value 0.76). The annual incidence rate of PH development was 11.3 per 1000 person-years. Details of analysis of factors associated with PH development in the current cohort is shown in table 4 and 5. During follow up, there were 54 patients with worsening tricuspid regurgitation, with incidence of 4.8%.

4.3.3. Secondary outcomes

In the multivariable Cox regression model (figure 2), it is shown that age is significantly and independently associated with the risk of developing PH, with 7% increasing risk for every year of age (hazard ratio [HR] 1.07, 95% confidence interval [CI] 1.22-1.13, P <0.001). Left atrial area measured from 4-chamber view and moderate to severe mitral regurgitation at baseline are also correlated with significant outcome (HR 1.12, 95% CI 1.03-1.22, P=0.01; and HR 7.60, 95% CI 1.36-42.43 (P=0.02), respectively. Of note, the association of these variables remained stable after comprehensive adjustment for potential confounders (table 3).

4.4.Discussions

4.4.1. Major Findings

Pulmonary hypertension is debilitating condition that is considered infrequent. This cohort study of all de novo CIEDs using standardised data acquisition observes the following new information:

- The risk of PH development in patients undergoing CIED implantation were notable at 4.3% of cases, with annual event rate of 11.3 per 1000 person-years.
- Age is an independent predictor of PH development after CIED implantation procedures, with 7% increasing risk for every year of age.
- Left atrial area and severe mitral regurgitation at baseline are also independent predictors of significant outcome.

Permanent transvenous CIED implantation is a safe and widely used therapeutic intervention for cardiac arrhythmias. PH secondary to CIED has not been a standard complication considered after implantation. To the best of our knowledge, the present study is the first in literature that highlighted the incidence of the risk of PH in patients with implanted transvenous CIEDs. We were also able to highlight the predictors attributed to the outcome.

4.4.2. CIED related thromboembolic phenomenon

CIED-induced right atrial thrombus is a rare condition that has not been widely described. Although serious clinical thrombotic and embolic complication was reported in 0.6-3.5% of cases,[207] silent lead thrombosis can occur in up to 30% of all patients with implanted CIED.[77] Seeger et al reported 15% of patients have small perfusion defects on pulmonary scintigraphy within 14 days after pacemaker placement.[202] Two mechanisms that contributed to lead-related

thrombus formation is that: (1) erosion and thrombosis result from a foreign material that may traumatize the lining of the vessel; and (2) thrombotic material developed upon the surface of a catheter left within the vascular system. Few published post mortem case reports in CIED patients showed that there were formation of thrombotic material encasing the lead within right ventricle as well as superficial mural thrombus at the superior vena caval-right atrial junction contributed from the intravenous lead.[208,209] In addition, the presence of foreign material may have an impact in hyperactivity of platelet due to direct contact of platelet with artificial surface.[210]

The higher percentage of ventricular pacing may itself increased thrombogenesis. Loss of atrioventricular synchrony causes numerous atrial contractions against closed atrioventricular valves which then lead to intra-atrial stasis. Lau et al reported that this phenomenon may also exaggerate spontaneous systemic-platelet activation in this population and subsequently increase the risk of thromboembolic events. In addition, it has been well described that increased ventricular pacing may result in atrial fibrillation which lead to more risk of thromboembolism.

A recent study of data from an international prospective registry shows that only 74.8% of patients with PH have previously confirmed PE,[211] suggesting a role of sub-clinical pulmonary emboli in development of PH. PE results in increased pulmonary vascular resistance due to unresolved embolic obstruction, fibrosis and remodelling of pulmonary arterial branches. This may further present clinically as right heart failure.[212] Right heart failure is the most common cause of hospitalization in patients with PH and is associated with a 14% in-hospital mortality rate.[213]

4.4.3. Predictors of pulmonary hypertension outcome

Although the current study clearly documents an incidence of PH after CIED implants, the exact pathogenesis of this observation remains unknown. Indeed, whether it is directly correlated with thrombus formation or other comorbidities associated with thromboembolic disease, remains unclear. Our study demonstrated that age is one of the strong independent predictors of PH development. Elderly patients are at increased risk of venous stasis and thrombus formation, not only because 70% of elderly was shown to have more than one predisposing comorbidities, but decreased mobility in elderly alone also increases the risk for thrombosis. Furthermore, elderly is predisposed to develop AF due to the "negative" atrial remodelling resulting from the increase of fibrous and adipose tissue leading to intra-atrial conduction abnormalities, which also increases thromboembolic risk.

Additionally, our study also demonstrated that left atrial size and moderate to severe mitral regurgitation as significant predictors of PH. Enlargement of atrial area may reflect pre-existing atrial mechanical and electrical remodelling. Ventricular pacing is reported to worsen atrial enlargement and decrease in atrial wall motion.[214] Furthermore, few reports showed that loss of intraventricular and atrioventricular synchrony from ventricular pacing worsening of mitral regurgitation that may lead to the progression to PH.[215] Presence of atrial remodelling could further promote AF, leading to more thromboembolic risk.

In this study, the use of oral anticoagulation also did not seem to give significant benefit to protect against PH development. However, it should be taken into consideration that oral anticoagulation was given for those with underlying higher thromboembolic risk profile. This may also explain no significant difference in the presence comorbidities with high

thromboembolic risk such as atrial fibrillation, ventricular pacing, or high CHA_2DS_2-VASc score, as most of patients in this groups have received oral anticoagulation as recommended by guidelines. Therefore, the relationship between the comorbidities, oral anticoagulation and PH development could not be justified.

4.4.4. Study Limitations

Our study was an observational cohort study of real-world clinical patients. Therefore, there was an understandable attrition and availability of echocardiographic data. The study utilised echocardiography to measure pulmonary artery systolic pressure (PASP). Right heart catheterization was not performed; therefore, our assessment was limited to patients with sufficient tricuspid valve regurgitation to allow the estimation of PASP. Thus, we could not determine whether the true incidence of PH is even higher.

Our study may have been underpowered to further evaluate the relationship between anticoagulation in correlation with pulmonary hypertension induced by thrombosis. Unfortunately, a few numbers of patients undergoing CIED implants were lost to follow-up. Prior studies demonstrated the evidence of thrombosis in this population, raising the possibility that there is a small effect that is difficult to demonstrate unless a very large number of participants included.

4.5.Conclusion

The risk of development of PH is increased in patients with transvenous CIEDs. Age, left atrial size, and mitral regurgitation are clinical predictors of PH development after CIED implantation. This outcome potentially leads to a fatal condition, therefore annual echocardiogram may be warranted in its early identification.

4.6.Tables

Table 1. Echocardiographic assessment of pulmonary hypertension. IVC=inferior vena cava; PH=pulmonary hypertension; RA= right atrium; TRV=tricuspid regurgitation velocity[205]

A. Probability of PH based on TRV			
	Peak TRV (m/s)	**Presence of other PH signs**	**Likelihood of PH**
	≤2.8 or not measurable	No	Low
	≤2.8 or not measurable	Yes	Intermediate
	2.9-3.4	No	
	2.9-3.4	Yes	High
	≥3.4	Not required	
B. Other echocardiographic sign suggesting PH			
	Ventricles	**Pulmonary artery**	**IVC and RA**
	Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
	Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm
		PA diameter > 25 mm	

Table 2. Baseline clinical characteristics

Variables	Median (interquartile range) N (%)
Baseline	
Age (median,IQR)	73.0 (64.6-80.1)
Gender – female (n, %)	438 (38.6)
Body mass index (median,IQR)	27.6 (24.9-31.4)
Comorbidities	
Hypertension	646 (57.1)
Diabetes Mellitus	203 (17.9)
Hyperlipidemia	359 (31.7)
Hyperthyroid	4 (0.4)
Ischemic cardiomyopathy	56 (4.9)
Hypertrophic cardiomyopathy	13 (1.1)
Dilated cardiomyopathy	63 (5.6)
Stroke	54 (4.8)
Obstructive sleep apnea (OSA)	161 (14.2)
Deep vein thrombosis/pulmonary embolism	30 (2.7)
Myocardial infarction	80 (7.1)
Coronary bypass surgery	56 (4.9)
Cardiac valve surgery	37 (3.3)
Excessive alcohol intake	55 (4.9)
Renal impairment	3 (0.3)
Medication	
Oral anticoagulation - Warfarin - Direct oral anticoagulant	405 (35.8) 254 (22.4) 145 (30.5)
Other medication	
- Calcium channel blocker	29 (2.6)
- Angiotensin receptor blocker	258 (22.8)
- ACE inhibitor	354 (31.3)
- Beta blocker	399 (35.2)
- Amiodarone	37 (3.3)
- Digoxin	45 (4.0)
- Flecainide	76 (6.7)
- Sotalol	75 (6.6)
Arrhythmias	
- Atrial fibrillation • Paroxysmal • Persistent	487 (43.0) 220 (19.4) 126 (11.1)
• Atrial tachycardia	41 (3.6)
- Atrial flutter	84 (7.4)
Atrial fibrillation ablation	109 (9.6)

Table 3. Device and echocardiographic parameters at baseline

Variables	Median (interquartile range) N (%)
Device characteristics	
Atrial pacing percentage (median,IQR)	42.3 (5.3-79.6)
Ventricular pacing percentage (median,IQR)	11.2 (1.0-64.4)
Atrial fibrillation burden (median,IQR)	0.1 (0.0-1.0)
Type of devices	
- Pacemakers	801 (70.8)
- Implantable Cardioverter Defibrillator	151 (13.3)
- Cardiac resynchronization Therapy-Pacing	30 (2.7)
- Cardiac resynchronization Therapy-Defibrillator	61 (5.4)
Number of leads	
- 1	125 (11.0)
- 2	847 (74.8)
- 3	84 (7.4)
Echocardiographic parameters at baseline	
LV ejection fraction (median,IQR)	57 (51-64)
- Normal	789 (69.7)
- Mild dysfunction	116 (10.2)
- Moderate dysfunction	66 (5.8)
- Severe dysfunction	53 (5.2)
Right atrial area (median,IQR)	16.4 (13.5-20.2)
Left atrial area (median,IQR)	20.7 (17.1-25.1)
Left ventricular end diastolic volume (median,IQR)	88.3 (68.5-120.3)
Left ventricular end systolic volume (median,IQR)	35.3 (25.0-55.3)
Valves	
- Moderate to severe mitral regurgitation	92 (8.1)
- Moderate to severe aortic regurgitation	18 (1.6)
- Moderate to severe mitral stenosis	68 (6.0)
- Moderate to severe aortic stenosis	24 (2.1)
- Moderate to severe tricuspid regurgitation	72 (6.4)

Table 4. Univariate Cox regression analysis

Variables	PH (-)	PH (+)	HR (95% CI)	P Value
Baseline				
Age (median,IQR)	72.7 (64.6-79.8)	77.0 (66.2-85.4)	1.049 (1.020-1.080)	0.001
Female (n,%)	415 (38.5)	22 (41.5)	1.247 (0.719-2.164)	0.433
Body mass index (median,IQR)	27.3 (24.6-31.3)	27.3 (24.7-30.7)	0.967 (0.916-1.022)	0.234
Comorbidities				
Hypertension (n,%)	624 (62.7)	22 (51.2)	0.655 (0.359-1.193)	0.169
Diabetes Mellitus (n,%)	192 (19.3)	11 (25.6)	1.531 (0.770-3.047)	0.242
Hyperlipidemia (n,%)	348 (35.0)	11 (25.6)	0.493 (0.242-1.004)	0.051
Hyperthyroid (n,%)	3 (0.1)	0 (0)	1.000 (0.996-1.004)	0.883
Cardiomyopathy (n,%)	107 (9.9)	11 (20.8)	1.948 (0.993-3.821)	*0.052*
Ischemic cardiomyopathy (n,%)	49 (5.0)	7 (16.7)	2.636 (1.138-6.107)	0.024
Dilated cardiomyopathy (n,%)	58 (5.9)	5 (11.9)	2.275 (0.892-5.802)	0.085
Stroke (n,%)	53 (5.3)	1 (0.1)	0.502 (0.069-3.650)	0.496
Obstructive sleep apnea (OSA) (n,%)	160 (16.1)	1 (2.3)	0.131 (0.018-0.954)	0.045
OSA requiring CPAP (n,%)	64 (6.5)	0 (0)	0.045 (0.0-12.947)	0.283
Deep vein thrombosis/pulmonary embolism (n,%)	30 (3.0)	0 (0)	0.073 (0.0-356.522)	0.545
Chronic pulmonary disease (n,%)	26 (2.6)	3 (7.0)	2.999 (0.925-9.723)	0.067
Myocardial infarction (n,%)	74 (7.4)	6 (14.0)	1.806 (0.745-4.382)	0.191
Coronary bypass surgery (n,%)	54 (5.4)	2 (4.7)	0.902 (0.218-3.732)	0.886
Cardiac valve surgery (n,%)	35 (3.4)	2 (5.4)	1.339 (0.399-5.772)	0.642
Excessive alcohol intake (n,%)	55 (5.6)	0 (0)	0.046 (0.0-24.473)	0.336
Renal impairment (n,%)	3 (0.3)	0 (0)	0.050 (0.0-2.822)	0.841
CHA_2DS_2-VASc score (n,%)				
- 0	2 (2.0)	97 (98.0)	(ref)	
- 1	9 (5.0)	172 (95.0)	3.923 (0.491-31.375)	0.298
- ≥2	32 (4.2)	726 (95.8)	4.321 (0.590-31.627)	0.157

Table 4. Univariate Cox regression analysis (cont.)

Variables	PH (-)	PH (+)	HR (95% CI)	P Value
Medication				
Oral anticoagulation (n,%) - Warfarin - Direct oral anticoagulant	 237 (24.1) 143 (14.6)	 17 (40.5) 2 (4.8)	 1.505 (0.807-2.807) 0.707 (0.165-3.033)	 0.199 0.641
Aspirin (n,%)	328 (33.4)	17 (40.5)	1.308 (0.7062.424)	0.394
Calcium channel blocker (n,%)	28 (2.9)	1 (2.4)	0.728 (0.100-5.295)	0.754
Angiotensin receptor blocker (n,%)	247 (25.2)	11 (26.2)	1.167 (0.584-2.332)	0.662
ACE inhibitor (n,%)	337 (34.3)	17 (40.5)	1.114 (0.595-2.087)	0.736
Beta blocker (n,%)	379 (38.6)	20 (47.6)	1.630 (0.886-2.997)	0.116
Amiodarone (n,%)	35 (3.6)	2 (4.8)	1.564 (0.377-6.483)	0.538
Digoxin (n,%)	38 (3.9)	7 (16.7)	4.225 (1.869-9.548)	0.001
Flecainide (n,%)	72 (7.3)	4 (5.3)	1.103 (0.393-3.097)	0.852
Sotalol (n,%)	73 (7.4)	2 (4.8)	0.528 (0.127-2.193)	0.380
Arrhythmias				
- Atrial fibrillation (n,%) • Paroxysmal • Persistent	463 (45.3) 212 (21.6) 123 (12.5)	24 (50.0) 8 (19.0) 3 (7.1)	1.097 (0.619-1.946)	0.750
Atrial tachycardia (n,%)	39 (4.0)	2 (4.7)		
Atrial flutter (n,%)	78 (8.0)	6 (14.3)	1.808 (0.760-4.304)	0.181
Atrial fibrillation ablation (n,%)	116 (10.8)	8 (15.1)	0.755 (0.440-1.295)	0.307

Table 5. Univariate Cox regression analysis of device and echocardiographic parameters

Variables	PH (-)	PH (+)	HR (95% CI)	P Value
Device characteristics				
Atrial pacing percentage (median,IQR)	50.4 (7.9-83.0)	31.0 (3.0-74.7)	0.991 (0.982-1.001)	0.069
Ventricular pacing percentage (median,IQR)	8.4 (1.0-61.7)	29.2 (1.2-84.3)	1.005 (0.997-1.014)	0.218
Atrial fibrillation burden (median,IQR)	0.1 (0.0-1.5)	0.4 (0.0-9.8)	1.010 (0.993-1.028)	0.254
Type of devices			1.018 (0.580-1.788)	0.949
- Pacemakers	768 (95.9)	33 (4.1)		
- Implantable Cardioverter Defibrillators	143 (94.7)	8 (5.3)		
- Cardiac resynchronization Therapy-Pacing	30 (100)	0 (0)		
- Cardiac resynchronization Therapy-Defibrillator	56 (91.8)	5 (8.2%)		
Number of leads			0.806 (0.443-1.466)	0.480
- 1	116 (11.5)	8 (16.7)		
- 2	809 (80.0)	35 (72.9)		
- 3	86 (8.5)	5 (10.4)		
Echocardiographic parameters at baseline				
LV ejection fraction	57.5 (52-64)	50.5 (40-63)	0.977 (0.959-0.996)	0.024
Right atrial area	16.1 (13.4-19.9)	20.0 (16.4-22.7)	1.092 (1.076-1.115)	<0.001
Left atrial area	18.8 (15.2-22.8)	26.1(20.1-40.3)	1.088 (1.043-1.134)	<0.001
Left atrial diameter	3.9 (3.5-4.4)	4.6 (3.6-4.9)	1.770 (1.155-2.713)	0.009
Left ventricular end diastolic volume	88.1 (68.5-120.1)	96.1 (67.0-125.7)	1.005 (0.999-1.011)	0.111
Left ventricular end systolic volume	35.1 (24.9-54.2)	39.5 (25.3-76.0)	1.007 (1.002-1.013)	0.013
Valves				
- Moderate to severe mitral regurgitation	81 (7.5)	11 (20.8)	4.367 (2.231-8.546)	0.002
- Moderate to severe aortic regurgitation	16 (1.5)	2 (3.8)	5.908 (1.415-24.664)	0.015
- Moderate to severe mitral stenosis	61 (5.7)	7 (13.2)	1.795 (0.246-13.085)	0.564
- Moderate to severe aortic stenosis	23 (2.1)	1 (1.9)	3.531 (1.584-7.871)	0.002

4.7.Figures

Figure 1. Study enrolment flowchart

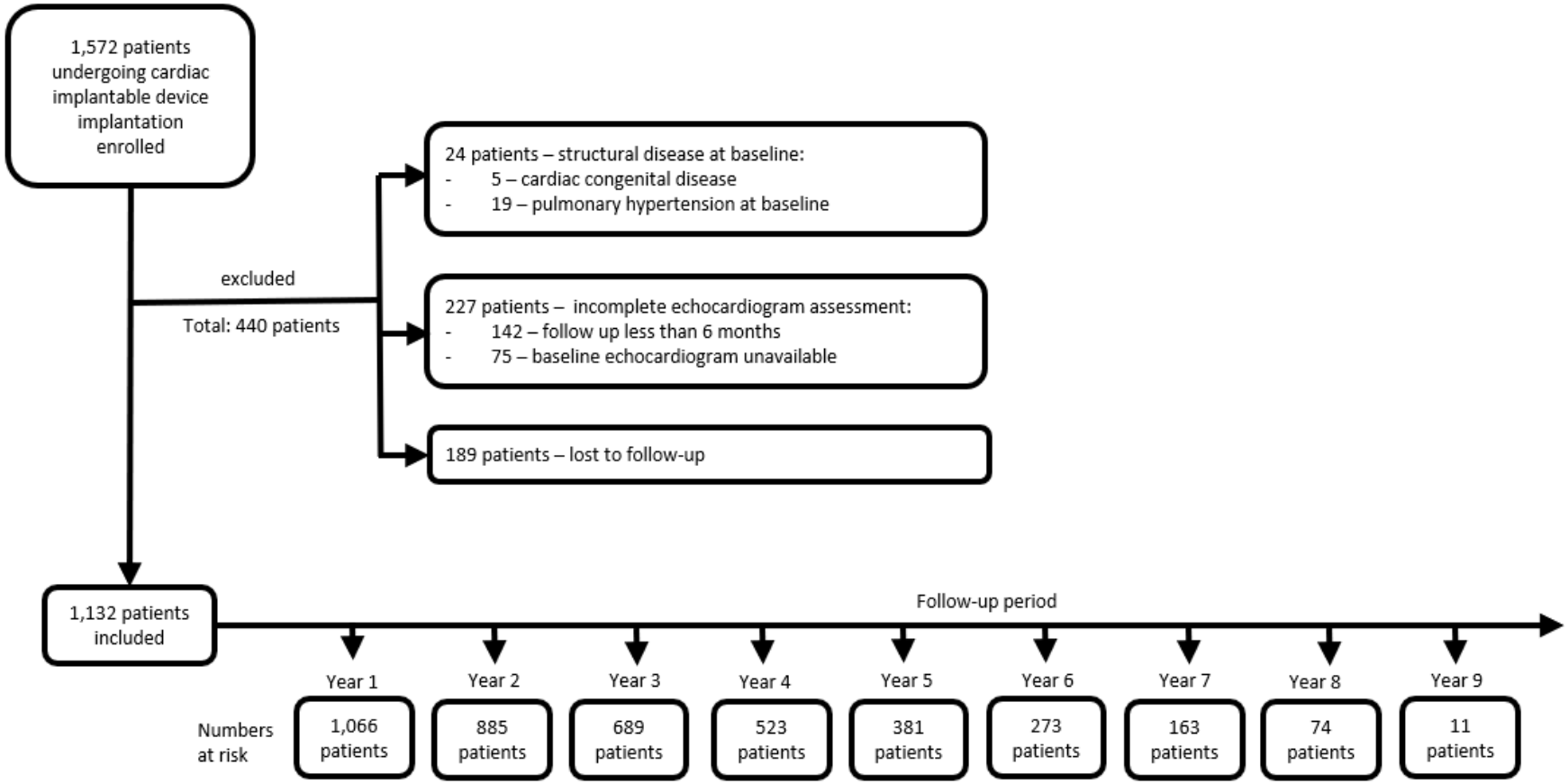
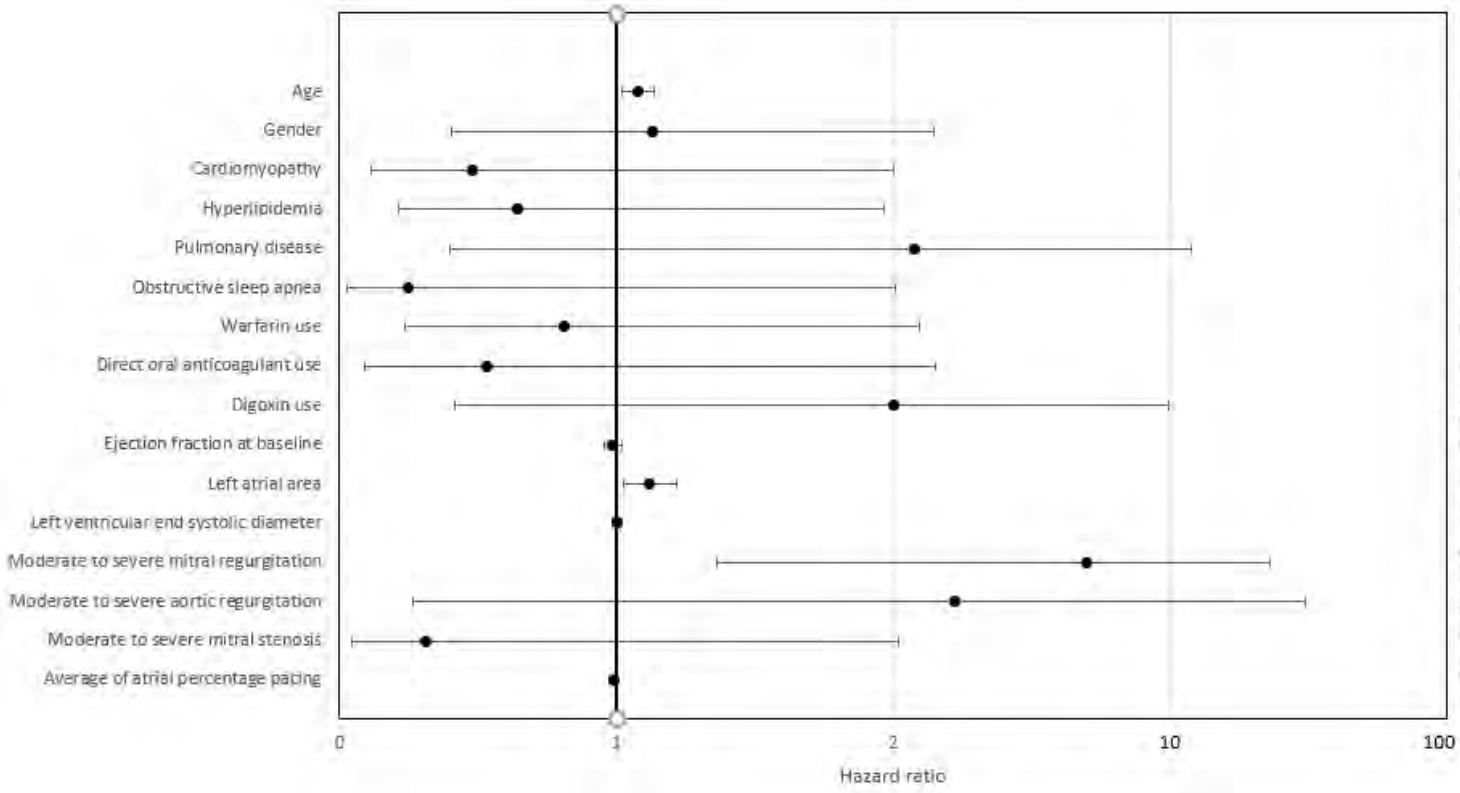


Figure 2. A forest plot of the hazard ratio and 95% confidence intervals associated with variables considered in the multivariable Cox regression analyses with time to the primary endpoint (pulmonary hypertension) as the dependent variable. Circles represent the hazard ratio and the horizontal bars extend from the lower limit to the upper limit of the 95% confidence interval of the estimate of the hazard ratio.



	Hazard ratio (95% CI)	P Value
Age	1.08 (1.02-1.13)	0.006
Gender	1.13 (0.41-3.16)	0.814
Cardiomyopathy	0.48 (0.11-2.01)	0.314
Hyperlipidemia	0.64 (0.21-1.97)	0.439
Pulmonary disease	2.61 (0.4-17.05)	0.318
Obstructive sleep apnea	0.25 (0.03-2.05)	0.195
Warfarin use	0.81 (0.23-2.78)	0.736
Direct oral anticoagulant use	0.53 (0.09-3.24)	0.496
Digoxin use	2.04 (0.42-9.95)	0.380
Ejection fraction at baseline	0.99 (0.95-1.02)	0.384
Left atrial area	1.12 (1.03-1.22)	0.010
Left ventricular end systolic diameter	1.00 (0.99-1.02)	0.635
Moderate to severe mitral regurgitation	7.60 (1.36-42.43)	0.021
Moderate to severe aortic regurgitation	3.80 (0.27-54.2)	0.326
Moderate to severe mitral stenosis	0.31 (0.05-2.14)	0.237
Average of atrial percentage pacing	0.99 (0.97-1.00)	0.109

CHAPTER 5

Implication of Ventricular Pacing Burden and Atrial Pacing Therapies on the Progression of Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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5.1.Introduction

The association between atrial fibrillation (AF) and sinus node dysfunction (SND) has long been identified, with incidence rate of AF being 125 per 1000 person-years in SND patients, ten times higher than normal population.[216] In SND patients undergoing pacemaker implant, newly diagnosed AF occurs in up to 68% of the population, and the prevalence of permanent AF reaching 15% over the long term.[217]

A number of randomized controlled trials (RCTs) have investigated the role of cardiac pacing algorithms in reducing the burden of AF.[45] The MINERVA trial, which analysed the impact of managed ventricular pacing (MVP), atrial preventive pacing (APP), and atrial antitachycardia pacing (aATP) therapies, demonstrated the beneficial effect of combination of these algorithms.[45] However, in contrast to prior studies, this study suggested that MVP alone did not prevent AF progression.[45] Here we undertook a systematic review and meta-analysis of RCTs to evaluate the impact of: (1) reducing percentage of ventricular pacing (RedVP); and (2) role of APP and aATP therapies as compared to conventional DDD pacing in preventing the progression of AF.

5.2.Methods

5.2.1. Literature search and data sources

This meta-analysis was registered on PROSPERO (CRD42018092280) and conducted in accordance with the PRISMA statement. Searches were conducted using the medical scientific electronic databases, PUBMED and EMBASE, from inception to 26th March 2018 to identify all relevant studies. The search used keywords of ‘sick sinus syndrome’ OR ‘sinus node dysfunction’ AND ‘atrial fibrillation’ AND ‘atrial arrhythmia’ AND atrial tachyarrhythmia’

AND ‘managed ventricular pacing’ AND ‘minimize ventricular pacing’ AND ‘antitachycardia pacing’ AND ‘atrial overdrive pacing’ AND ‘atrial preference pacing’ AND ‘atrial pacing therapies’ AND ‘ventricular pacing’ AND ‘dual chamber (DR) pacing’ AND ‘single chamber (SR) pacing’ AND ‘physiologic pacing’. The search was limited to the articles in English language and human studies. All references obtained through the databases were reviewed manually. Bibliographies of retrieved articles and reviews were searched manually for additional publications.

5.2.2. Inclusion and exclusion criteria

Citations were included if the studies met following criteria: (i) RCTs; (ii) studies enrolled patients with standard indication of de novo permanent pacemaker implantation; (iii) compared the impact of physiologic pacing or pacing algorithms on AF, with continuous variable outcomes mentioned in mean and standard deviation. Studies comparing SR VVI pacing, or performed in specific population were excluded.

5.2.3. Study selection and quality assessment

Eligibility assessment was performed independently by two investigators (DAM, TAA). Disagreements were resolved by consensus. Selected publications for RedVP and APP+ATP algorithms were analyzed for the outcome of progression to non-paroxysmal AF – defined as number of patients who progressed to non-paroxysmal AF. Studies investigating APP algorithms were analysed for the following outcomes: (1) premature atrial complexes (PACs) burden – defined as the daily average number of PACs (measurement unit was standardized to numbers/day); (2) AF burden – defined as daily average duration of the observed time in AF (measurement unit was standardized to minutes/day); (3) AF episodes – defined as daily numbers of episodes in (measurement unit was standardized to numbers/day); and (4) adverse

events. Data extraction sheet was developed based on Cochrane Consumers and Communication Review Group's data extraction template and refined accordingly.

Assessment of the methodological quality of clinical trials included was performed according to the Cochrane Collaboration's tool for assessing risk of bias.

5.2.4. Statistical Analysis

Statistical analysis was performed using the software package RevMan (version 5.0), provided by the Cochrane Collaboration. Outcomes were pooled using DerSimonian and Laird random effects model. Odd ratio (OR) or hazard ratio (HR) as appropriate and 95% confidence interval were reported as the outcomes are dichotomous. The heterogeneity was tested using Mantel-Haenszel chi^2 test and the I^2 statistics. Significant heterogeneity was considered if the I^2 was more than 50%. Statistical significance was set at $P < 0.05$.

5.3. Results

5.3.1. Search and synthesis of the literature

A total of 754 English citations were identified after the initial search combined with supplementary hand searches. 655 studies were excluded after screening the title and abstract. After secondary review of the full-text articles in the remaining 99 selected studies, 72 studies were excluded because they were review articles, case reports or case series, cohort studies, or conference abstracts. 5 studies were excluded due to comparing DR pacing with SR VVI pacing. 21 RCTs with a total of 8,336 participants were finally included in this review. The various studies were categorized based on the type of algorithm utilized: (1) 3 studies assessed the benefit of reducing ventricular pacing in DR pacemaker.[47,113,218] (2) 14 studies assessed the role of APP algorithm alone.[117,119,120,219-229] (3) 4 studies comparing a combination of pacing

algorithms for prevention of AF progression (3 studies comparing aATP+APP algorithm,[128,230,231] and 1 study comparing RedVP+APP+aATP algorithm).[45] *Figure 1* shows the data search and selection methodology. The details of the studies and baseline characteristics of the participants are provided in *table 1 and 2*.

5.3.2. Algorithms for reducing ventricular pacing and atrial pacing therapies

RCT studies of RedVP algorithm are available for MVP™ (Medtronic) and SafeR™ algorithm, however HR analysis are only available for MVP™ studies.[45,47,113] To date, no RCTs have been published for Rhythmiq (Boston Scientific) or VpSupression (Biotronik). The details of RedVP algorithms are described in *figure 2*.

Atrial pacing therapies include all device algorithms aimed to (1) prevent AF by continuous overdrive atrial pacing or supressing PAC triggers; or (2) to terminate any detected atrial arrhythmias. The RCT studies for atrial overdrive algorithm (figure 3) are available across all manufacturers, however, the RCTs evaluated in non-parametric analysis were excluded (*table 1)*. For AF termination, atrial ATP therapy (Medtronic) works by delivering a series of atrial pacing at an atrial cycle length shorter than the detected arrhythmia, with two programmable options available (Burst ATP and Ramp ATP). First generation of ATP therapy only allowed redelivery after an unsuccessful ATP therapy after expiration of a time interval.[128,230,231] However, the newer generation, the Reactive ATP, allows multiple deliveries on the detection of change in the rhythm regularity or cycle length (*figure 4*).[45]

5.3.3. Effects of reduced cumulative percentage of ventricular pacing (Reduced VP%) in AF progression

Four studies (3,648 patients) reported on the impact of VP% on AF progression. The median age of participants was 73.5 years [IQR 72.4-73.7]. Overall 327 patients (19.2%), progressed to non-paroxysmal AF over a span of 22.0 [IQR 18.5-44.5] months.[45,47,113,218]

Reduced ventricular pacing was obtained by two approaches; (1) SR AAI pacing, or (2) RedVP algorithm. The median VP% in the RedVP versus conventional DDD was 1% (IQR 0%-9.1%) and 65% (IQR 65%-99%), $p<0.05$, respectively. The overall analysis shows that AF progression occurred in 16.5% [95% CI 7.2-28.9] of patients with low VP% (<10%) and 25.0% [95% CI 15.5-35.7] of those with high VP% (≥ 10%). Despite the trend towards reduction to non-paroxysmal AF, no significant difference in AF progression resulted from reduced VP% (HR 0.80, 95% CI 0.57-1.13; p value 0.21, I^2=66%; *figure 5A*).

A sub-analysis was performed to assess the role of RedVP algorithm.[45,47,113] This analysis revealed a similar non-significant reduction in progression in in patients with RedVP algorithm as compared to conventional DDD pacing (HR 0.66, 95% CI 0.40-1.10; p=0.11, I^2=64%; *figure 5B*), with the absolute number of 19.1% [95% CI 7.3-33.0] and 21.4% [95% CI 12.1-32.6], respectively. The median VP% in the two groups was 1% (IQR 1%-9.1%) and 53% (IQR 53%-99%), $p<0.05$, respectively.

5.3.4. Role of atrial preventive pacing and antitachycardia therapy in AF outcome

Eighteen studies (5,854 patients) examined the role of APP and aATP therapies on the outcome of AF.[45,117,119,120,128,219-231] Of these, 14 analysed APP alone,[117,119,120,219-229] three studies analysed the role of APP+aATP algorithms,[128,230,231] and one study investigated role of

RedVP+aATP+APP as compared to conventional DDD programming.[45] The median age of the patients was 73.7 [IQR 72.5-76.0] years and they were followed up for a median period of 30 [IQR 30-37] months.

APP resulted in an increase in atrial pacing (18 studies, 5,854 patients, APP vs conventional: 90.7%±4.7% and 51.6%±15.5, p<0.001). The VP% was high and did not differ between the two groups (8 studies, 4,125 patients, APP vs conventional: 54.6%±15.8% and 53.7%±15.9%, p=0.07). APP algorithm reduced the daily PACs burden (6 studies, 363 patients, APP vs conventional: 608±340 per day vs 1,492±989 per day; MD [Mean Difference] -1117.74, 95% CI [-1852.36-(-383.11)], p=0.003, I^2=67%, *figure 6A*).[119,219,223,226,227,229] Despite this, there was no reduction in AF burden with APP as compared to conventional DDD at 89.4±75.2 min/day vs 83.6±71.6 min/day, respectively (11 studies, 1,213 patients, MD 8.20, 95% CI -5.39-21.80, p=0.24, I^2=17%, *figure 6B*). Additionally, there was non-significant reduction in the number of AF episodes in APP group (6.1 per day [95% CI -0.06-12.2) vs conventional DDD pacing (11.6 per day [95% CI -3.2-26.5]), respectively (9 studies, 961 patients, MD 0.00, 95% CI -0.24-0.25; p value 0.98, I^2=0%; *figure 6C*).

Four studies with a total of 1,645 patients reported the role of APP+aATP in AF outcome. The pooled analysis of these studies showed that a combination of APP+aATP therapy did not prevent the progression to non-paroxysmal AF as compared to coventional DDD pacing (OR 0.65, 95% CI 0.36-1.14; p = 0.13; I^2=61% *figure 6D*).

5.3.5. Atrial and Ventricular Pacing and Atrial Fibrillation

A total of 4,504 patients (13 studies) were included in the studies investigating APP algorithms,[117,119,120,219,221-229] showing a weak corellation between with the increase of AP%

and AF burden (r=0.22, p value <0.01, figure 7A). On the other hands, 9 studies (7,099 patients) reported VP% and incidence of AF progression.[45,47,113,128,218,221,222,224,230] The pooled analysis of these studies showed a moderate correlation between VP% and AF progression incidence (r=0.4, p value <0.01, figure 7B).

5.3.6. Adverse events

Table 3 demonstrates the adverse events during follow-up period. No significant difference in the incidence of algorithm related serious events either in the studies investigating RedVP or atrial pacing therapy algorithms. One study reported intolerance to APP pacing[26] and inappropriate AT/AF detection[222] in 1.1% and 23% of patients, respectively. Furthermore, early battery depletion was significantly higher in the group of APP algorithms (1 study, 4.4% patients).[222]

5.3.7. Risk of bias within studies

The risk of bias assessment in the included studies is shown at table 4. All the studies were RCT with appropriate study methodology. Twelve studies were crossover trials,[119,120,219,220,223,225-229,231] while thirteen studies were parallel trials.[45,47,113,117,128,218,221,222,224,230] Most trials were single blinded, except one which was double blinded[221] and nine studies did not mention the blinding method. No study was excluded on the basis of quality.

5.4.Discussions

The principal findings of this meta-analysis are:

(1) Reducing ventricular pacing burden to <10% by utilising pacing algorithms failed to reduce the progression of AF;

(2) Although the PAC burden (AF trigger) was suppressed by APP pacing, it did not translate to reduction in either burden or severity of AF.

It is not clear whether specific populations would benefit from atrial therapies and is an area of ongoing research.

5.4.1. Ventricular pacing and risk of AF progression

This meta-analysis confirms the effectiveness of RedVP algorithms in minimising ventricular pacing. RedVP algorithms such as MVP™ *(see figure 2)* allows the pacemaker to operate primarily in AAI/R mode and automatically switches into DDD/R mode upon detection of loss of AV conduction. Despite the reduction in VP%, physiologic pacing did not demonstrate a reduction in the AF. Ventricular pacing causes asynchronous activation of the ventricles,[232] regional myocardial blood flow abnormalities that may induce ischemia,[233] and valvular regurgitation due to papillary muscle derangement leading to ventricular dysfunction.[233] This failing heart may cause atrial structural and electrical remodelling, and increased propensity for AF.[234] These changes are more pronounced in populations with heart failure. Despite the detrimental effects of high VP%, the current RedVP algorithms failed to demonstrate a significant reduction in AF progression possibly due to (1) fewer patients with heart failure in the included studies and (2) non-physiological AV intervals in patients with impaired AV conduction.[235] Non-physiological AV delay results in ventricular preload reduction, diastolic mitral regurgitation,[235] atrial stretch and remodelling creating a substrate for AF These changes are more pronounced in populations with heart failure. Despite the detrimental effects of high VP%, the current RedVP algorithms failed to demonstrate a significant reduction in AF progression possibly due to (1) fewer patients with heart failure in the included studies and (2) non-physiological AV intervals in patients with impaired AV conduction.[235] Non-

physiological AV delay results in ventricular preload reduction, diastolic mitral regurgitation,[235] atrial stretch and remodelling creating a substrate for AF[218] and offset the benefits of reducing ventricular pacing[236] and underlines the need for further improvement of algorithms designed to reduce VP%. Nevertheless, the RedVP pacing strategies decrease likelihood of heart failure and improve battery longevity. and offset the benefits of reducing ventricular pacing[236] and underlines the need for further improvement of algorithms designed to reduce VP%. Nevertheless, the RedVP pacing strategies decrease likelihood of heart failure and improve battery longevity.[158]

5.4.2. Atrial pacing therapy algorithms to prevent AF

The role of APP algorithms with respect to AF prevention remains controversial. Few studies have revealed that majority of paroxysmal AF episodes are initiated by PACs or bradycardia.[114] Intuitively, continuous overdrive pacing obtained by APP algorithm has been proposed to prevent AF by suppressing PACs. On the other hands, there has been data suggesting that atrial pacing increments might have a direct relationship with increasing AF incidence.[237] Although AF suppression was reported in observational cohorts,[238] this has not borne out in RCTs.[45,117,119,120,128,220,222-231] This meta-analysis confirmed that APP algorithm reduced but did not eliminate PAC burden. The resultant reduction in PAC burden did not translate into reduction in AF burden or AF episodes. The lack of benefit may be related to high number of VP% (>50%) reported in most of the included studies, which probably negates the beneficial effects of supressing AF triggers. Supporting data shown by sub-analysis of PIPAF study demonstrated that reduction in AF burden with APP was limited to the sub-group with low VP%.[120] Similar evidence was also shown in the MINERVA[45] that demonstrated AF reduction was limited to the group where with a combination of reactive aATP, APP and MVP algorithms.[128] In addition, atrial pacing alone may also play a role in the progression of AF.

Pacing from right atrial appendage causes significant non-physiological atrial conduction which lead to LA dysfunction, and thus may further increase AF propensity.[237] Furthermore, the patients in the APP studies had several risk factors for AF *(table 2)*.[239] In absence of risk factor modification, APP therapies supress AF triggers but may not be sufficient to prevent AF progression.

5.4.3. Safety profile of minimising ventricular pacing and atrial pacing therapies algorithms

The general concern related to RedVP algorithm is the risk of prolonged ventricular pauses during the AV block searching period that could potentially lead to symptomatic events, especially in pacing dependent patients. In this study, we found a low incidence of ventricular pauses in the RedVP group, without any significant difference in the adverse events between both group. Similarly, no significant difference in the clinical events were found in APP studies. However, the increment of AP% achieved by APP algorithm is shown to be significantly contribute to early battery depletion, as demonstrated by a recent published study that showed pacing burden increments from 50% to 100% could reduce up to 22% (~2.5 years) of total device longevity.[240] In addition, a significant number of false AT/AF detection was also reported. This finding emphasized that adjudication in evaluating device-based AF burden is a mandatory.

5.4.4. Study Limitation

Substantial heterogeneity amongst the studies is potentially the most important limitation in our study. A possible source of this heterogeneity could be different population and even discrepancies in the outcome definitions in the included studies. Some studies detected AF outcome from mode switch events, while others as atrial tachyarrhythmia events. There was

also lack of adjudication for AF events. In addition, AF burden measurement was presented in different units, varying from percentage time in AF to duration in AF. Furthermore, the heterogeneity may have resulted due to differences in the design and duration of the studies.

5.5.Conclusions

This meta-analysis of RCTs demonstrates that despite the ability of pacing algorithms in reducing PAC burden, atrial pacing therapies do not appear to produce meaningful benefit in the reduction of AF burden or AF progression. In addition, minimising ventricular pacing using the current algorithms failed to significantly reduce risk of AF progression. The use of these algorithms is considered safe; however, the decision of their utilisation should be made on individual basis. Further research is required to refine the algorithms and to define the subset of patients benefitting from such strategies.

5.6.Tables

Table 1. Characteristic of studies**.**

Study	Study design	Number of participants	Follow-up period (months)	Device	Groups	Atrial pacing percentage (mean/median)		Ventricular pacing percentage (mean/median)		Endpoints definition
						Intervention	Control	Intervention	Control	
AAI vs DDD										
DANPACE[218]	Parallel, multicenter	1,415	65	Not specified	AAI vs DDD	NA	NA	0	65	• Numbers of chronic atrial fibrillation
RedVP vs conventional programming										
The long-MinVPACE[113]	Parallel, single blind, multicenter	33	17	Vitatron, ELA Medical, Medtronic	RVP/AAISafer/ MVP vs conventional programming	NA	NA	5.8	74	• Number of persistent AF
SAVE PACe[47]	Parallel, single-blind, multicenter	1,065	20	Medtronic (Kappa700, Kappa900, EnPulse, EnRhythm)	MVP vs conventional programming	71.4	70.4	9.1	99	• Number of persistent AF

Atrial pacing therapies vs conventional programming										
ASSERT[222]	Parallel, single blind, multicenter	2,343	30	St Jude Medical (Identity ADx DR [5386/5380])	AFSupression™ vs conventional programming	88	40	54	52	• AT/AF > 6 minutes
APP[119]	Crossover, multicenter	42	1	Guidant [1280]	APP™ vs conventional programming	86.6	45.6	88	94	• PAC – a spontaneous atrial interval > 750 ms and an adjacent sense interval <25% or less • Total duration of AF episodes
SAFE[224]	Parallel, single blind, multicenter	385	37	St Jude Medical (Identity ADx DR [5386/5380])	AFSuppression™ vs conventional programming	92	56	26	26	• Number of persistent AF • AT/AF detection – 225 bpm • AF burden - %
DeVoogt et al[220]	Crossover, single blind, multicenter	177	3	St Jude Medical (Integrity AFx DR [5346], Identity ADx DR [5376], or Trilogy DAO [5346])	Atrial overdrive algorithm vs conventional programming	92.7	51.2	53.7	61.2	• AF burden – cumulative mode switch duration • AMS detection – 225 bpm

Kale et al[228]	Crossover, single center	17	3	Medtronic AT500 and Guidant Pulsar Max II	APP+ARS+PMOP (Medtronic) and APP™ (Guidant) vs conventional programming	99.7	66	NA	NA	• AF detection – A rate >180bpm for 8 cycles • AF burden – AF relative to total time from pacemaker strorage
Miki et al[226]	Crossover, single center	17	0.5	Medtronic (Thera DR)	APP vs conventional programming	97.7	52.3	NA	NA	• PAC counts • AF – mode switch >15 secs
Padeletti et al[229]	Crossover	46	3	Medtronic (Thera DR)	CAP vs conventional programming	96 (RAAP) and 97 (IASP)	76 (RAAP) and 83 (IASP)	NA	NA	• AF detection – A rate >180bpm, more than 1 min
PAFS[227]	Crossover, multicenter	182	1	Vitatron Selection 900 and T70	RS vs conventional programming	81.7	41.1	50	53.2	• AF detection – A rate >200 bpm, for 6 V beats (Selection 900) or >5 secs (T70)
PIPAF[120]	Crossover, single blind, multicenter	55	6	ELA Medical (Chorum 7334 or Talent DR 213)	SRO+PEPS+APAC vs conventional programming	98	86	67	67	• ATA burden – cumulative mode switch duration

Ricci et al[219]	Crossover, multicenter	61	2	Medtronic Thera DR 7940/7960	CAP vs conventional programming	96	77	NA	NA	• AF burden – AMS duration • Number of PAC counts per day
Lam et al[223]	Crossover, single center	15	2	Medtronic Thera DR (model 7940 or 7960)	APP vs conventional programming	86	57	NA	NA	• Number of PAC counts
ADOPT[117]	Parallel, single blind, multicenter	288	6	St Jude medical (Trilogy DR+/DAO [2360L or 2364L] or Integrity AFx (5346])	AF Supression™ vs conventional programming	92.9	67	NA	NA	• AF – a minimum of 30 s of continuous irregular rate. • AMS episode > 1 min
Levy[225]	Crossover, single blind, single center	27	6	ELA Medical Chorum	Atrial overdrive vs conventional programming	72	60	NA	NA	• Number of patients with further paroxysmal AF • Total duration of time pacemaker in fallback mode
SAFARI[221]	Parallel, single blind, multicenter	555	64	Vitatron Selection 9000	PPT vs conventional programming	96	58	46	55	• AF detection – adjudicated

										by trained reviewers before randomization • AF burden – number of hours in AF per day
Combined algorithm vs conventional programming										
MINERVA[45]	Parallel, single blind, multicenter	1,166	24	Medtronic (Enrhythm)	MVP+APP+aATP vs MVP vs conventional programming	95.6	89.4	46.6	59.9	• Number of permanent AF
Gillis et al[128]	Parallel, single center	71	36	Medtronic AT 500/501	Prevention (APP+ARS+PMOP) +aATP vs conventional programming	98	0	NA	NA	• Number of permanent AF • AT/AF burden – hours of AF per day
FACET[231]	Cross-over, single blind, multicenter	38	6	Medttronic AT500	APP+aATP vs conventional programming	98	75	99	98	• Number of permanent AF AT/AF burden – hours of AF per day
ATTEST[230]	Parallel, multicenter	370	3	Medtronic AT500	Prevention (APP+ARS+PMOP) +aATP vs conventional programming	93	70	2	53	• Number of permanent AF AT/AF burden – hours of AF per day

A: atrial; aATP: atrial Antitachycardia pacing; AF: atrial fibrillation; APAC:Acceleration after premature atrial complexes; APP (Boston Scientific/Guidant): Atrial Pacing Preference; APP (Medtronic): Atrial Preference Pacing; ARS: Atrial Rate Stabilization; ATA:Atrial tachyarrhythmias CAP: Consistent Atrial Pacing; IASP: Inter-atrial Septal Pacing; MVP:Managed ventricular pacing; NA: not available; PEPS:Post-extrasystolic pause suppression; PMOP: Post Mode Switch Overdrive Pacing; PPT: Preventive pacing therapies; RAAP: Right Atrial Appendage Pacing; RS:Rate soothing; SRO: Sinus rhythm overdrive; V: ventricular

Table 2. Baseline Characteristic of participants

Study	Age (Mean/ median)	Left Ventricular Ejection Fraction (Mean/median)	Hyper-tension (%)	Diabetes Mellitus (%)	Ischemic Heart Disease (%)	Heart Failure (%)
Single vs dual chamber						
DANPACE[218]	73.5	-	34.1	9.6	13.3	12.2
RedVP algorithm						
The long-MinVPACE study[113]	74.8	61.7	44.0	4.6	30.3	-
SAVE PACe trial[47]	72.4	58.1	73.3	22.5	19.3	20.4
APP algorithm						
ASSERT[222]	76.0	-	100.0	-	16.0	-
SAFE[224]	70.7	65.3	51.7	16.6	18.9	6.2
ADOPT[117]	71.3	56.5	-	-	-	46.5
Levy et al[225]	69.0	-	27.0	-	30.0	10.0
APP[119]	70.0	-	-	-	-	-
deVoogt[220]	73.5	-	-	-	-	-
SAFARI[221]	72.5	-	82.5	-	27.0	-
Kale et al[228]	56.7	-	-	-	-	-
Miki et al[226]	71.7	-	-	-	-	-
Padeletti et al[229]	76.0	-	41.0	-	45.0	-
PIPAF[120]	68.0	-	-	-	-	-
Ricci et al[219]	75.0	-	31.0	-	7.0	3.0
Lam et al[223]	70.0	-	13.3	6.6	26.6	-
PAFS[227]	72.6	-	33.1	10.7	27.5	9.2
Combined algorithm						
MINERVA[45]	73.7	56.7	69.2	16.0	13.0	4.1
GIllis[128]	71.0	-	50.0	-	37.3	20.7
FACET[231]	62.0	-	26.0	-	3.0	47.0
ATTEST[230]	69.9	-	61.4	-	33.0	25.9

Table 3. Adverse events for Algorithm vs Conventional Pacing Group

Adverse events	Algorithm group % (95% CI)	Conventional group % (95% CI)	OR (95% CI)	P value
Death (3 studies)[45,117,218]	10.9 (0.56-31.83)	8.0 (0.001-29.03)	1.18 (0.86-1.63)	0.30
Lead problem - including dislodgement, fracture, perforation (2 studies)[45,117]	1.9 (0.02-8.44)	1.43 (0.48-9.26)	1.21 (0.42-3.51)	0.72
Infection (2 studies)[45,117]	0.38 (0.003-1.38)	0.29 (0.02-1.48)	1.57 (0.16-14.64)	0.69
Pneumothorax (1 studies)[117]	0.6	1.4		NS
Reduced ventricular pacing studies				
Algorithm related events (1 study)[45]	3 (1.5) ventricular pauses	2 (1.1) pacemaker mediated tachycardia		NS
Early battery depletion (1 study)[45]	1 (0.1)	0 (0)		
Atrial pacing therapy algorithm studies				
Intolerant to high rate pacing (1 study)[26]	3 (1.1)	0 (0)		NS
False positive of AT/AF detection (1 study)[222]	267 (23.0)	90 (7.7)		<0.001
Early battery depletion (1 study)[222]	52 (4.4)	29 (2.5)		<0.01

Value are provided as number (percentage); NS=non significant

Table 4. Summary table of study quality and assessment of risk of bias based on Cochrane.

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting Bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
1. AAI vd DDD						
DANPACE[218]	Low	Low	Not mentioned	Not mentioned	Low (intention-to-treat)	Low
2. RedVP vs DDD						
SAVE PACe trial[47]	Low	Low	Low (single)	Low	Low (intention-to-treat)	Low
The long-MinVPACE study[113]	Low	Not mentioned	Low (single)	Not mentioned	Low	Low
3. APP vs DDD						
ADOPT[117]	Low	Low	Low (single)	Not mentioned	Low (intention-to-treat)	Low
APP[119]	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Low	Low
ASSERT[222]	Low	Low	Low (single)	Not mentioned	Low	Low
deVoogt et al[220]	Low	Not mentioned	Low (single)	High	Low (intention-to-treat)	Low
Levy et al[225]	Low	Not mentioned	Low (single)	High	Low	Low
SAFE[224]	Low	Not mentioned	Low (single)	High	Low	Low

SAFARI[221]	Low	Low	Low (single)	Low	Low	Low
Kale et al[228]	Low	Low	Not mentioned	Not mentioned	Low	Low
Miki et al[226]	Not mentioned	Not mentioned	Not mentioned	High	Low	Low
Padeletti et al[229]	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Low	Low
PIPAF[120]	Low	Not mentioned	Low (single)	Not mentioned	Low	Low
Ricci et al[219]	Low	Not mentioned	Not mentioned	Not mentioned	Low	Low
Lam et al[223]	Low	Not mentioned	Not mentioned	Not mentioned	Low	Low
PAFS[227]	Low	Not mentioned	Not mentioned	Not mentioned	Low	Low
4. Combined						
MINERVA[45]	Low	Low	Low (single)	High	Low (intention-to-treat)	Low
Gillis[128]	Low	Not mentioned	Not mentioned	Low	Low	Low
FACET[231]	Low	Not mentioned	Low (single)	High	Low	Low
ATTEST[230]	Low	Not mentioned	Not mentioned	Low	Low	Low

5.7.Figures

Figure 1: CONSORT diagram showing search methodology.

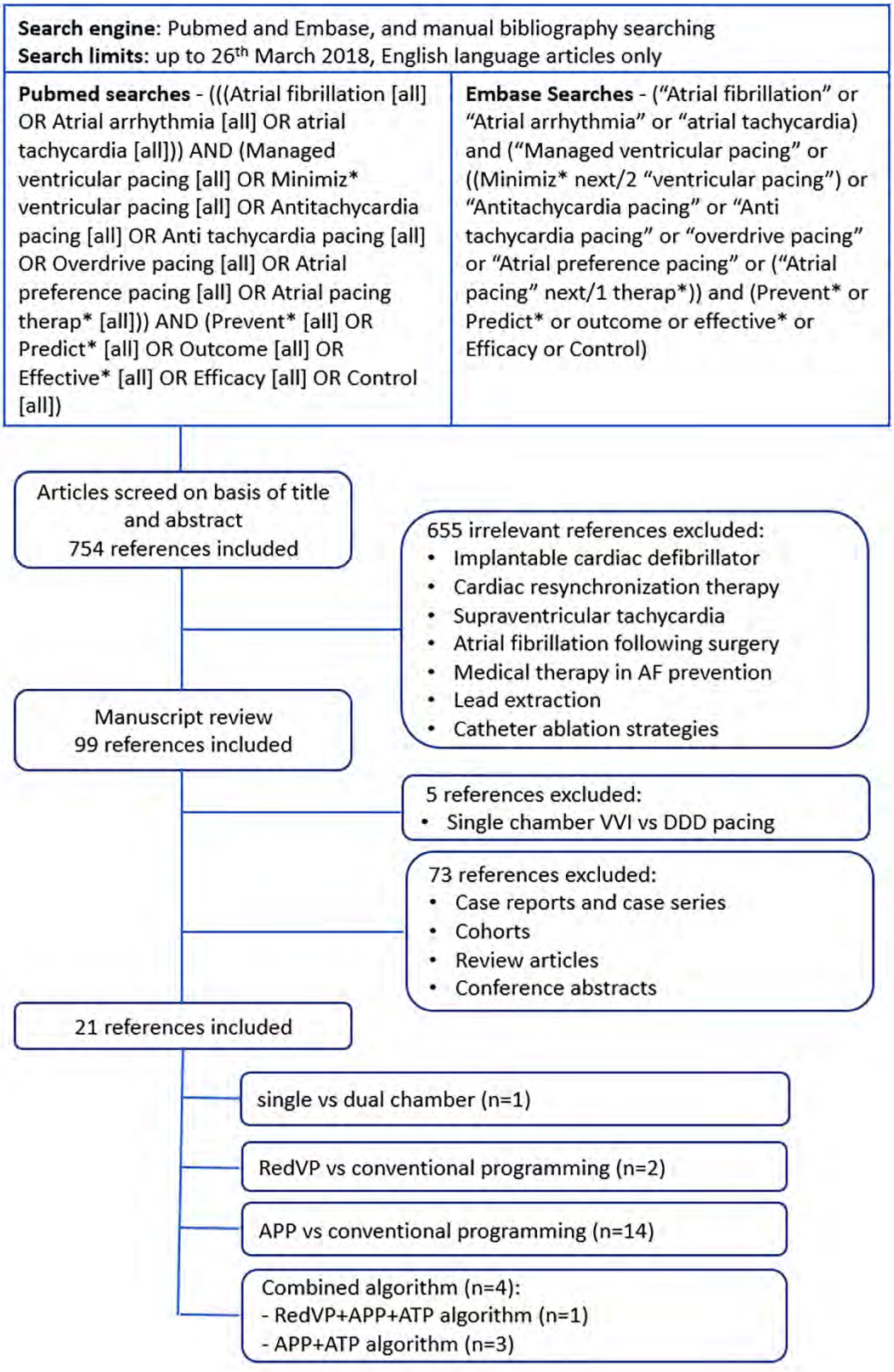


Figure 2: Detail of Reducing Ventricular Pacing (RedVP) Algorithms as per manufacturers
*: No RCT available to date; **: Included RCT studies; *** RCTs available, no Hazard Ratio shown
A: Atrial; AP: atrial pacing; AS: atrial sensing; AV: atrioventricular; BS: Boston Scientific; SJM: St Jude Medical; MVPTM: Managed Ventricular Pacing; V: Ventricular; VP: ventricular pacing; ventricular sensing

Criteria	Biotronik	BS	LivaNova	Medtronic	SJM	Vitatron
RedVP algorithms						
	Vp Supression®*	RYTHMIQ™*	SafeR™***	MVP™**		
Standard mode	DDD	AAI (+ VVI backup)	AAI	AAI (+VVI backup)	N/A	N/A
Switch criteria	• In DDD mode - progressive intervals after X cycles (programmable) up to 128 mins, then repeat every 20 hours • If x consecutive VS is met (programmable for 1-8 cycles) – switch to ADI	Longer V-V interval (>150 ms) than A-A in 3 out of 11 beats	• AVB 1° – 6 consecutive beats of prolonged PR interval • AVB 2° – 3 AS/AP without VS within 12 A cycles • AVB 3° – 2 consecutive AS/AP without VS • Pause – No VS within programmable interval (up to 4 s)	No VS in 2 out of 4 atrial intervals		
AV conduction search interval	In ADI mode – AV delay is extended up to 450 ms for 8 cycles	Using AV hysteresis algorithm to search AV conduction for 25 cycles	After 100 VP cycles	Progressive intervals after 1 min (2,4,8,.... Min) up to 16 hours, then every 16 hours		
Switch back criteria to standard mode	• A programmable number of cycles without VS • 2 consecutive cycles without VS • No VS for ≥ 2 secs	<2 of last 10 cycles are VP events	Detected 12 spontaneous VS	Detected VS event following A		

Figure 3: Detail of Atrial Pacing Therapy Algorithms as per manufacturers
*: Included RCT studies; ** RCTs available, continuous variable shown in geometric mean
A: Atrial; AP: atrial pacing; APP (BS): Atrial Pacing Preference; APAC: Acceleration after premature atrial complexes; APP (Medtronic): Atrial Preference Pacing; ARS: Atrial Rate Stabilization; AS: atrial sensing; AV: atrioventricular; BS: Boston Scientific; SJM: St Jude Medical; PEPS:Post-extrasystolic pause suppression; PMOP: Post Mode-switch Overdrive Pacing; RS:Rate soothing; SRO: Sinus rhythm overdrive; V: Ventricular; VP: ventricular pacing; ventricular sensing

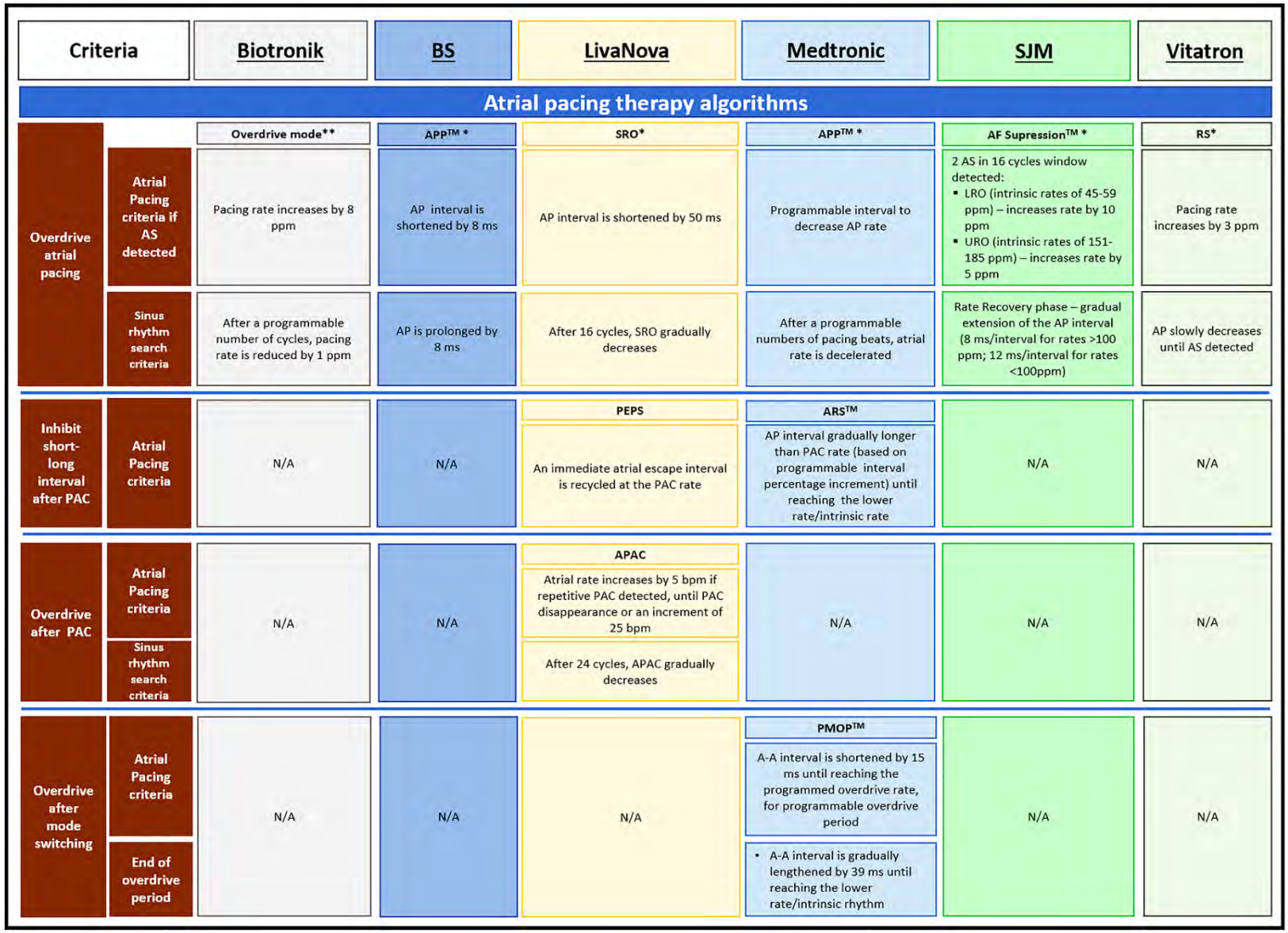

Criteria
Biotronik
BS
LivaNova
Medtronic
SJM
Vitatron
Atrial pacing therapy algorithms
Overdrive atrial pacing
Atrial Pacing criteria if AS detected
Overdrive mode**
APP™ *
SRO*
APP™ *
AF Supression™ *
RS*
Pacing rate increases by 8 ppm
AP interval is shortened by 8 ms
AP interval is shortened by 50 ms
Programmable interval to decrease AP rate
2 AS in 16 cycles window detected:
LRO (intrinsic rates of 45-59 ppm) – increases rate by 10 ppm
URO (intrinsic rates of 151-185 ppm) – increases rate by 5 ppm
Pacing rate increases by 3 ppm
Sinus rhythm search criteria
After a programmable number of cycles, pacing rate is reduced by 1 ppm
AP is prolonged by 8 ms
After 16 cycles, SRO gradually decreases
After a programmable numbers of pacing beats, atrial rate is decelerated
Rate Recovery phase – gradual extension of the AP interval (8 ms/interval for rates >100 ppm; 12 ms/interval for rates <100ppm)
AP slowly decreases until AS detected
Inhibit short-long interval after PAC
Atrial Pacing criteria
N/A
N/A
PEPS
An immediate atrial escape interval is recycled at the PAC rate
ARS™
AP interval gradually longer than PAC rate (based on programmable interval percentage increment) until reaching the lower rate/intrinsic rate
N/A
N/A
Overdrive after PAC
Atrial Pacing criteria
Sinus rhythm search criteria
N/A
N/A
APAC
Atrial rate increases by 5 bpm if repetitive PAC detected, until PAC disappearance or an increment of 25 bpm
After 24 cycles, APAC gradually decreases
N/A
N/A
N/A
Overdrive after mode switching
Atrial Pacing criteria
End of overdrive period
N/A
N/A
N/A
PMOP™
A-A interval is shortened by 15 ms until reaching the programmed overdrive rate, for programmable overdrive period
A-A interval is gradually lengthened by 39 ms until reaching the lower rate/intrinsic rhythm
N/A
N/A

Figure 4: Atrial ATP therapy to terminate AT/AF

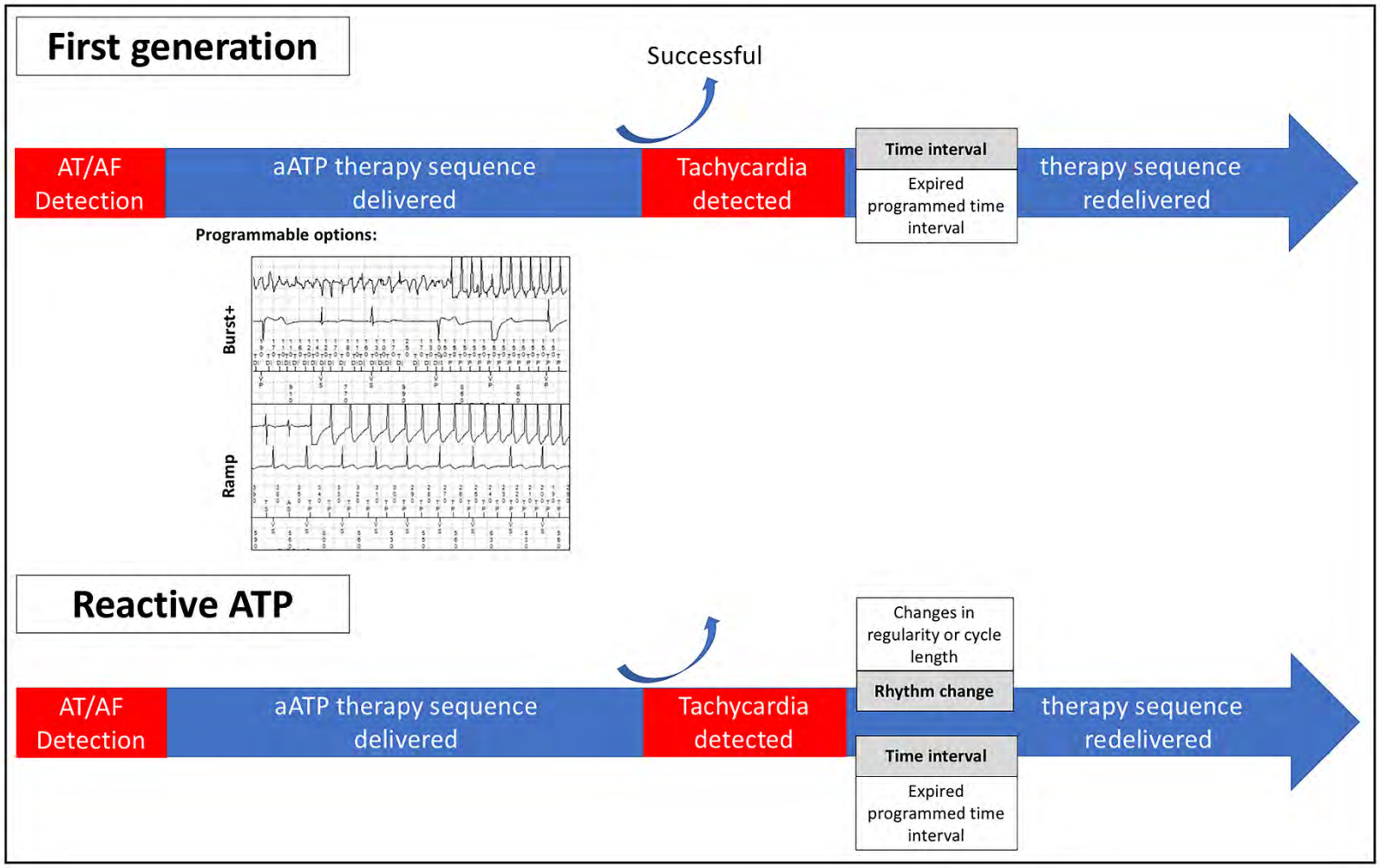


Figure 5: Ventricular pacing burden and progression to non-paroxysmal AF. A) Comparison of group with low VP% (< 10%) versus high VP% (≥10%); B) Sub-analysis of group with RedVP algorithm versus DDD. Effect size presented as hazard ratio (HR).

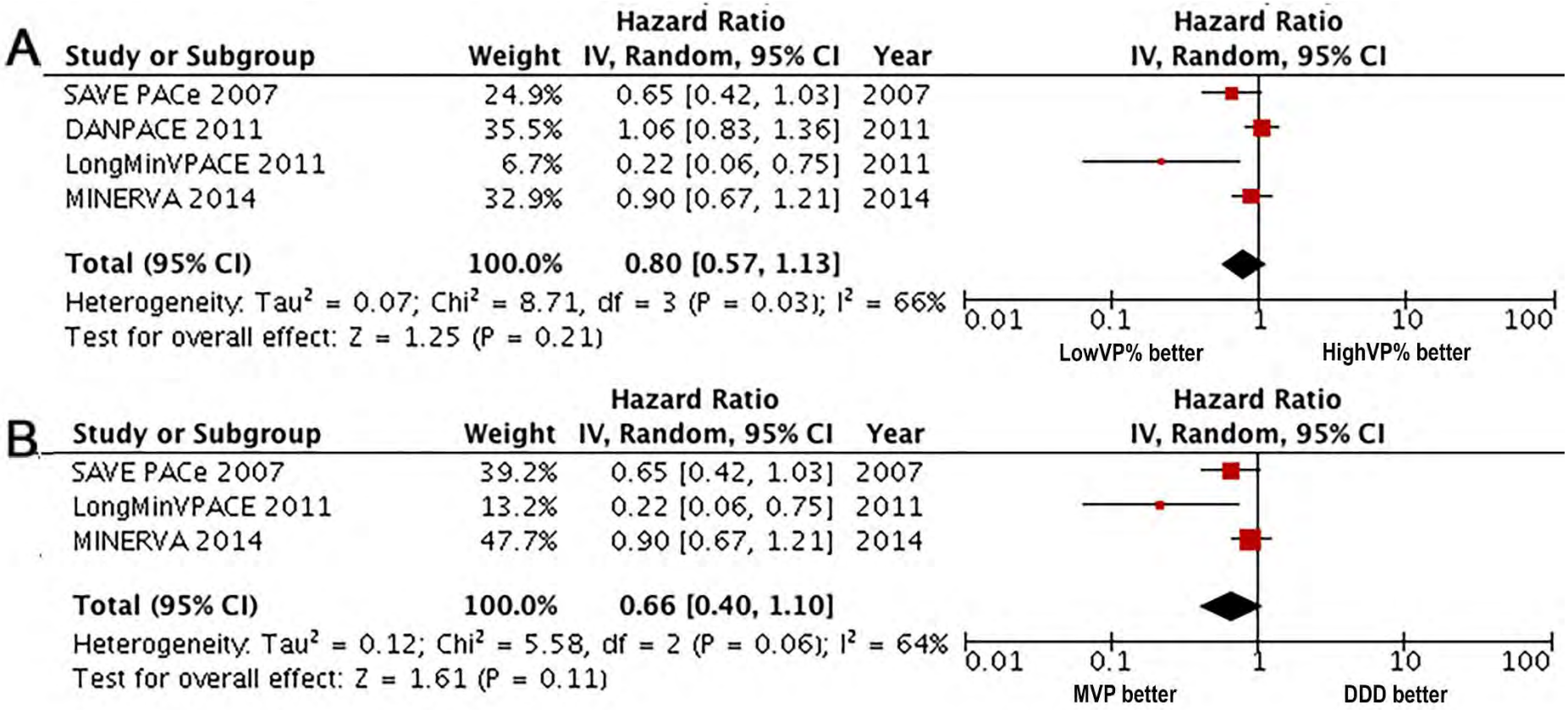


Figure 6. Comparison of APP algorithm versus conventional programming in dual chamber pacemakers. A) The daily premature atrial complexes (PACs) burden; B) AF burden (minutes/day); and C) Daily numbers of AF episodes; D) Comparison of APP + aATP with conventional programming in DR pacemakers for progression from paroxysmal to non-paroxysmal AF. Effect size of in fig 6A-C are presented as mean difference (MD) and 6D as OR.

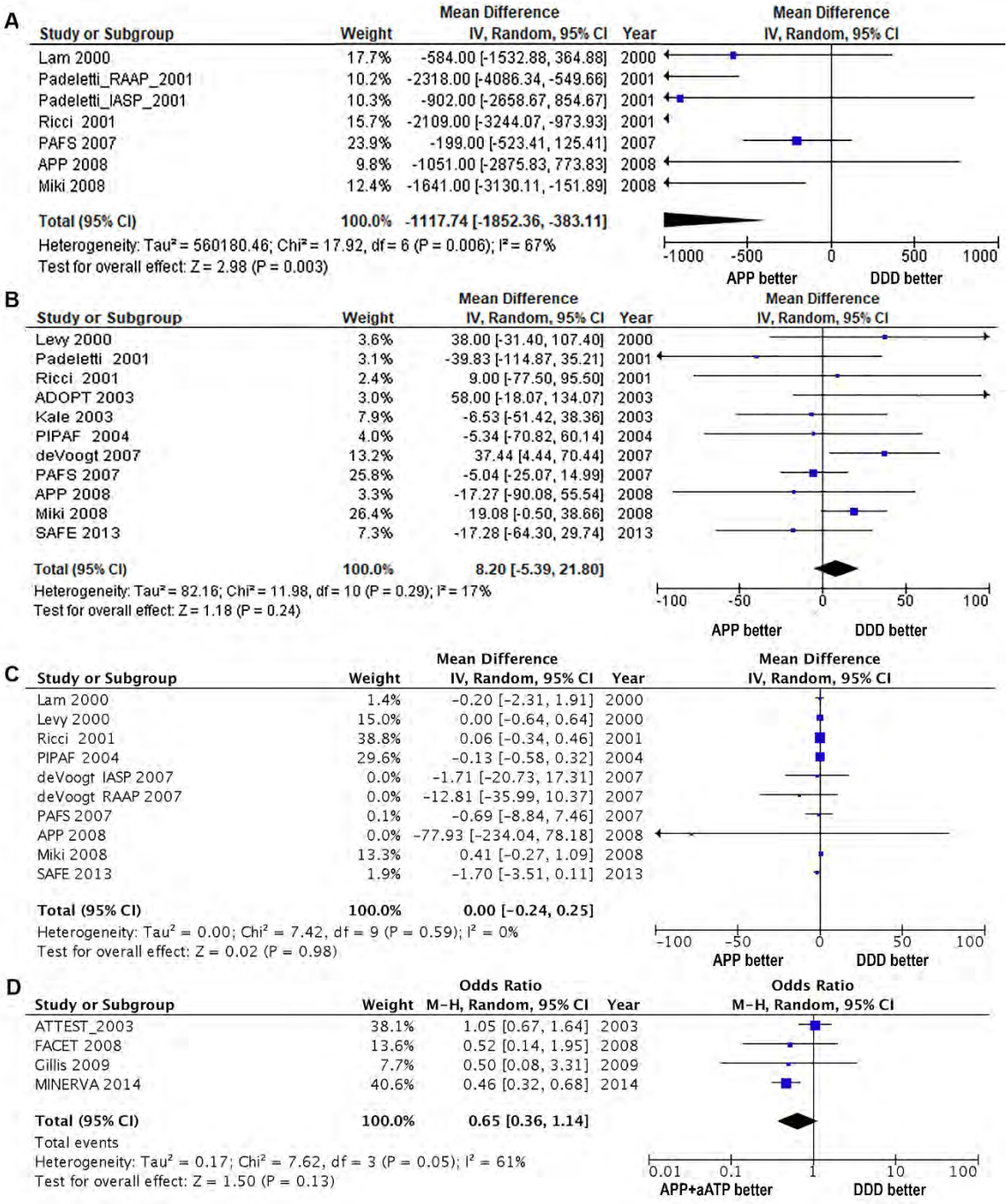
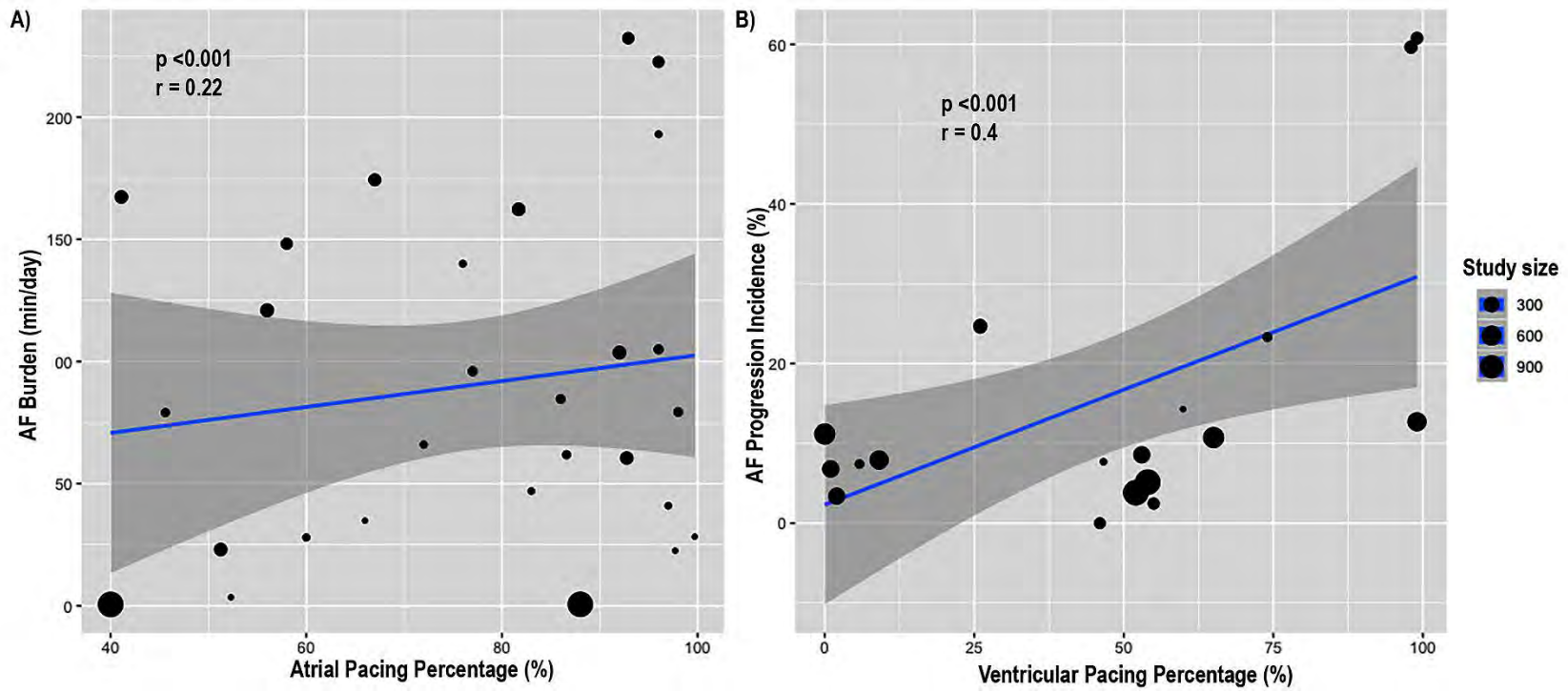


Figure 7. Relationship between atrial pacing and ventricular pacing burden with atrial fibrillation

A) Weighted linear regression of AP% and AF burden; B) Weighted linear regression of VP% and incidence of AF progression.



CHAPTER 6

Clinical Effectiveness of Atrial Pacing Therapies in Sinus Node Disease After Atrial Fibrillation Ablation (CEASE-AF): A Pilot Study

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6.1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia associated with sinus node dysfunction (SND). Recent studies have suggested that the risk of AF development was five-fold higher in SND, with the prevalence ranged from 45% to 53%.[216,241] In SND patients, incidence of AF and chronic AF following pacemaker implantation is still at least 5% and 3%, respectively, while lifetime cumulative incidences is approximately 30 to 40% and 20%, respectively.[242] Pacing algorithms that minimize ventricular pacing in patients with sinus node disease have been demonstrated to reduce the risk of AF progression and have become the standard of care.[45,142]

Pacing algorithms to prevent AF include minimized ventricular pacing (MVP) that reduce ventricular pacing (VP) burden and atrial preventative pacing (APP) that may suppress atrial ectopy as a trigger, and therefore prevent AF episodes. In addition, atrial anti-tachycardia pacing (aATP) algorithm has been shown effective for a termination of atrial tachycardia or atrial flutter.[243] There have been mixed results with these studies. Whilst previous published RCTs evaluating APP and aATP individually failed to show any significant benefit in AF prevention,[122,127,128] the MINERVA study recently demonstrated a significant reduction in AF burden when combining these algorithms as compared to standard DDD algorithm (4 min/day vs 17 min/day, P value = 0.002, respectively).[45]

Catheter ablation of AF has emerged as a technique used for the maintenance of sinus rhythm. Unfortunately, one of the consequences that has been reported is the not infrequently evolving reentrant atrial tachycardias (AT) , ranging from 10% to 24%.[133,134] Here we hypothesised that the more organised rhythms that follow AF ablation may be amenable to device mediated therapies.

The aim of this study is to assess the efficacy of APP and aATP algorithm in termination of atrial tachycardia and prevention of AF progression in patients with pacemakers and prior AF ablation.

6.2. Methods

6.2.1. Study Design and participant selection

The CEASE-AF study was a randomized, single-blind, cross-over, pilot clinical trial designed to evaluate the effectiveness of atrial pacing therapies in reducing AF burden after AF ablation.

All patients provided written informed consent to the study protocol that was reviewed and approved by the Human Research Ethics Committees of the Royal Adelaide Hospital and the University of Adelaide, Adelaide, Australia. The study is registered at the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), with trial ID ACTRN12616001353482.

Patient eligibility criteria included: (1) Clinical evidence of sinus node dysfunction and having received a dual chamber pacemaker in with capability of atrial pacing therapies (including APP and aATP therapy); (2) AF ablation ≥ 3 months prior to recruitment; (3) AF/atrial arrhythmia burden <75%; (4) Non-dependent to ventricular pacing (VP%≤40%); and (5) ≥ 18 years of age.

Patients will be excluded from the study if one of the following criteria is met: (1) Presence of indication for cardiac resynchronization therapy; (2) Had < 12 months of life expectancy; (3) Cardiac surgery in the last six months, or expected during 10 months of study period; (4) A recent history of (< 1 year) or current malignancy; (5) advanced heart failure (NYHA class IV);

(6) end-stage chronic obstructive pulmonary disease or other severe life-threatening comorbidities within 3 months of diagnosis; or (7) unable to provide consent.

6.2.2. Study protocol

All patients received a Medtronic dual-chamber pacemaker with specific features of: (i) managed ventricular pacing (MVP) algorithm to reduce ventricular pacing; (ii) atrial preventative pacing therapies (APP), to prevent atrial tachyarrhythmias; and (iii) reactive atrial anti-tachycardia pacing (aATP). Following recruitment, all patients commenced a 1-month run-in period during which all pacemakers were programmed to MVP algorithm ON only to assess the eligibility. Eligible patients were randomly assigned in a 1:1 manner to control group and intervention group and followed up for 12 months. Following the first year, all patients were crossed over to the alternate group for another 12 months. The detail of the study protocol is shown in figure 1. Examination of clinical symptom as well as the device interrogation were performed after run-in phase (1 month after pacemaker implantation procedure) and during each follow up visit (every six months). Each patient was given a home monitoring system for monthly device download. Throughout the study all patients remained blinded to the programmed pacing mode.

6.2.3. Details of Device Programming

In the control group, MVP was enabled, while APP and aATP algorithms were OFF. All algorithms including MVP, APP, and aATP were ON in the intervention group. Specific details about device programming are described in Table 1.

MVP is provided by Managed Ventricular Pacing (MVP™ (Medtronic)) modes that promote intrinsic conduction by reducing unnecessary right ventricular pacing. These modes (AAI-

DDD or AAIR-DDDR) provide atrial-based pacing with ventricular backup, while monitoring AV conduction. If AV conduction is lost, the device is designed to switch to DDDR or DDD mode. Periodic conduction checks are performed, and if AV conduction resumes, the device switches back to AAIR or AAI mode. For transient loss of AV conduction, the device remains in the AAIR or AAI mode and provides a backup ventricular pace in response to an A-A interval that is missing a ventricular sense. If two of the four most recent nonrefractory A-A intervals are missing a ventricular event, the device identifies a persistent loss of AV conduction and switches to the DDDR or DDD mode. When MVP is operating in DDDR or DDD mode, all programmable parameters associated with DDDR or DDD mode apply. The device performs periodic one-cycle checks for AV conduction and the opportunity to resume AAIR or AAI therapy. The first check for AV conduction occurs after 1 minute. Subsequent checks occur at progressively longer intervals (2, 4, 8 … min) up to 16 hours and then occur every 16 hours thereafter. Depending on the patient's intrinsic rhythm and conduction, MVP allows V-V cycle variations and occasional pauses of up to twice the lower rate interval. When MVP is operating in AAIR or AAI mode, only the programmable parameters associated with AAIR or AAI mode apply. Ventricular backup paces occur following A-A intervals without a valid ventricular sense. The backup paces are timed 80 ms after the A-A escape interval. A ventricular sense that occurs within 80 ms after the A-A interval is considered invalid and does not inhibit the backup pace. Atrial pacing is inhibited and new VA escape intervals are started in response to PVCs and PVC runs after the A-A interval.[109]

The device also includes three types of pacing algorithms to prevent AT/AF recurrence, including atrial preference pacing (APP), atrial rate stabilization (ARS), and a post-mode-switch overdrive pacing mode (PMOP). APP responds to changes in the atrial rate by accelerating the pacing rate until it reaches a steady paced rhythm that is slightly faster than

the intrinsic rate, up to a programmed “maximum rate”. After each nonrefractory atrial sensed event, the device decreases the atrial pacing interval by the programmed “interval decrement” value. Beats continue at this elevated rate until the pacing rate exceeds the intrinsic rate, resulting in an atrial paced rhythm. The increased rate is sustained for the number of beats programmed as the “search beats” parameter. APP then decreases the pacing rate slightly (by 20 milliseconds; nonprogrammable) to search for the next intrinsic beat. This results in a dynamic, controlled, stairstep increase or decrease in the pacing interval, maintaining a pacing rate slightly above the intrinsic rate.[244] When ARS algorithm is enabled, at each atrial event (AS event, AP event, or pertinent AR event), the device calculates a new pacing interval, which is equal to the current pacing interval increased by the programmed “Interval Percentage Increment”. If the current pacing interval ends before the device senses an atrial event, the device delivers an atrial pace and recalculates its interval using the current atrial interval. The current pacing interval will be the shorter of the sensor rate interval or the calculated interval. The programmed Maximum Rate value provides a rate limit for operation of the feature. After a PAC, the calculated escape interval stabilizes the atrial rate and gradually slows it to the intrinsic rate, sensor-indicated rate, or programmed Lower Rate (whichever is attained first).[245] PMOP extends Mode Switch through a period of overdrive atrial pacing following the termination of an AT/AF episode. It gradually increases the pacing rate by decreasing the pacing interval in milliseconds per pulse, until the programmed overdrive rate has been reached. PMOP then continues DDI(R) pacing at the overdrive rate. When the Overdrive Period expires, the rate is gradually modulated until the lower rate or sensor rate is reached and the pacemaker switches back to the programmed mode.[246]

For episode termination, Reactive ATP™ allows for multiple deliveries of programmed atrial antitachycardia pacing (ATP) therapies during an atrial tachyarrhythmia episode in response to

either of the following events: (1) Rhythm Change, which allows detection of trial arrhythmia using both regularity and cycle length; and (2) Time Interval, which is based on the expiration of a programmed time interval. Two rate-adaptive options are available for aATP therapies, including Ramp and Burst+. Ramp therapy sequences consist of a programmable number of AOO pulses delivered at decreasing intervals. Burst+ therapy sequences consist of a programmed number of AOO pulses followed by 2 premature stimuli that are delivered at shorter intervals. VVI ventricular backup pacing is available during both Ramp and Burst+ pacing.[247]

6.2.4. Study outcomes

The primary outcome of this study is the number of patients free from AF, defined as patients with AF burden ≤0.1 hour per day. The secondary outcome of this study was the aATP efficacy based on atrial cycle length (ACL). The rhythm strips were adjudicated manually by a committee of experienced electrophysiologists blinded to the study randomisation.

6.2.5. Statistical Analysis

All the analysis was done based on the intention to treat analysis (ITT). Continuous variables are summarised using mean ± SD or median (interquartile range [IQR]) as appropriate, whereas the categorical variables using number (n) and percentage (%). Categorical variables were compared by chi-square or Fisher exact test. Normally of the data is tested using Shapiro-wilk test. To evaluate the effects of intervention on the AF events over 2 years, mixed-effects logistic regression models were fitted. Variables that were significant at univariate analysis and/or clinically relevant parameters such as age, gender, body mass index (BMI), and obstructive sleep apnoea (OSA), were included in the multivariate analysis. Odds ratios (OR) and their 95% confidence intervals were obtained. Non-parametric Kruskal–Wallis H test was used to

compare the ATP efficacy across the ACL zones. A p value < 0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS version 25 (IBM Inc, Armonk, NY, USA) and Stata 16.1.

6.3. Results

6.3.1. Patients characteristics

A total of 59 patients were enrolled in the study. After run-in period, 2 patients were excluded from the study due to eligibility (100 %VP) and 3 patients withdrew from the study before randomisation. The remaining 54 patients were randomised based on the protocol for 12-month time. After this period, eighteen patients refused to undergo the crossover period, therefore 36 patients were crossed over into the other group and followed up for another 12-month period.

The baseline characteristics are depicted in Table 2. Mean age of all included patients was 71.8 ± 6.8 years, with 20 patients (37.0%) were female. Mean of BMI was 28.5 ± 4.1 kg/m^2. No death or major cardiovascular events were documented during the study follow-up.

6.3.2. Atrial and ventricular pacing percentage

At baseline, the median of atrial pacing percentage was at 55.0% (IQR 18.7%-81.0%), while ventricular pacing percentage was 0.1% (IQR 0.1%-0.4%). There was significant increase in the number of atrial pacing percentage during the intervention group as compared to control group (95.2 (IQR 90.1-97.2) vs 55.0 (29.1-87.7), p value <0.001, respectively). On the other hand, MVP algorithm could supress ventricular pacing percentage to 0.1% (IQR 0.1%-1.8%) vs 0.1% (IQR 0.1%-0.6%), p value 0.980, respectively (figure 2).

6.3.3. Primary outcomes

Overall, there were 28 out of 43 patients (65.1%) in the intervention group and 24 out of 47 patients (51.1%) who were free from AF over each follow-up period. The 2-year follow-up clearly suggests significant reduction in the AF in the intervention arm compared to the control group. In the intervention group, there was a 41% reduction in AT/AF events (OR, 95% CI : 0.59, 0.43-0.83, p value 0.002) compared to control group after adjusting for the effects of age, gender, BMI, and OSA (figure 3).

6.3.4. Secondary outcomes

6.3.4.1. Atrial antitachycardia pacing therapy efficacy based on tachycardia cycle length

Figure 4 shows the efficacy of aATP therapy based on detected ACL during tachycardia. ACL was categorized according to detection windows of ACL from pacemaker report. It is demonstrated that in 12 months of follow-up, aATP was successful in 1,721 out of 4,365 atrial arrhythmia episodes (aATP efficacy of 39.6%). Of these, additional 1.4% of episodes (unresponsive to Ramp aATP) were terminated by Burst+ aATP therapy. In the analysis of aATP efficacy based on atrial cycle length zones, it is shown that aATP efficacy is significantly higher in zones with greater cycle length (Kruskal-Wallis H P value 0.038). Notably, the highest efficacy was seen in the zones between 400-449 ms (see figure 4).

6.4. Discussion

6.4.1. Major Findings

The principal findings of this study showed that in the subset of patients with SND and AF with previous history of AF ablation:

(1) Atrial preventative therapies, including atrial preventative pacing and aATP algorithms, significantly reduce AT/AF events, with a 40% reduction of AF events over 2 years period.

(2) aATP efficacy is significantly higher with the greater ACL zones, with highest efficacy seen in the zones between 400-449 ms.

To the best of our knowledge, this pilot study is the first study investigating the efficacy of AF prevention algorithms (MVP, atrial preventative pacing, and aATP) to reduce AT/AF events in the settings of SND patients with dual chamber pacemaker who had a history of AF ablation.

6.4.2. Recurrence of atrial tachyarrhythmias after atrial fibrillation ablation

Regardless of the techniques, RF ablation of AF may result in regular atrial tachycardias (ATs) or flutter, which is one of the most important proarrhythmic complications. It is reported that pulmonary vein isolation (PVI) achieved by placing circular lesions around the veins in the left atrial (LA) antrum with creation of additional lines in LA (e.g. mitral isthmus, and/or roof, or posterior lines) could increase the incidence of AT dramatically, ranging from 10% to 24 %.[133,134] The most common mechanism (73-82%) involves incomplete or recovered lesions and other anatomic obstacles from anatomic ablation approached, with additional lines and/or CFAE ablation, that create gap and trigger macroreentrant AT.[248] Atrial tachycardia or more organized arrhythmias are potentially more amenable to intervention by pacing. Our study enrolled all patients with persistent AF with previous AF ablation. At baseline, it is shown that 82.4% of patients were free from AT/AF episodes. No significant differences were found in the numbers of patients free from AF between intervention and control group.

6.4.3. Pacing modalities in post atrial fibrillation ablation

Over the years, a number of important clinical trials have reported on clinical outcomes associated with different cardiac pacing modalities. Some combinations of proprietary pacing algorithms designed to suppress AF burden by overdrive pacing and AF terminating algorithm have been shown to have conflicting results in the impact on AF burden in general populations of patients with pacemakers and paroxysmal AF. The earlier data investigating both APP+aATP only compared to DDD setting reported by Gillis et al demonstrated that these algorithms were associated with a reduction in overall AT/AF burden.[243] Nevertheless, other randomized studies of atrial ATP therapy in conjunction with three atrial pacing therapies designed for prevention of AF failed to demonstrate a significant benefit in AT/AF burden reduction, although aATP therapy reportedly successfully terminated 41% of AT/AF episodes.[128,230] MINERVA trial, a recent published study evaluated MVP algorithm on top of both atrial prevention algorithm features (MVP+DDDRP(APP+reactive aATP)), showed quite a promising result. This study compared these features (MVP+DDDRP) with DDDR or with MinVP alone in patients with bradycardia and previous atrial arrhythmias. Significant reduction of numbers of patients who developed persistent or permanent AF were shown in the MVP+APP+reactive aATP group as compared to MVP only or DDDR group, at 15.1% vs 25% vs 15,1% after 2 years period.[45]

Particularly in the subset of AF ablation patients, our study confirmed that APP and aATP therapies could significantly reduce AF events, with 40% reduction as compared to control group. Our hypothesis is that the aATP efficacy would be higher than general paroxysmal AF considering that organised AT/AFl are the most common atrial tachyarrhytmia associated with recurrence. Previous study reports that efficacy of aATP therapy in terminating AT or AFl episodes have been varied from 37-60%.[243,249] In addition, episodes initially detected as AF is

shown to be less likely to be terminated by aATP therapy compared with episodes detected as AT. Our study showed aATP efficacy of 39.6%, which is about similar to general AF population in patients with PPM reported in the previous studies. Median P-P interval apparently is shown to be one of the major and independent determinants of aATP efficacy. Boriani et al demonstrated an increasing aATP efficacy with a longer ACL, especially with ACL > 200 miliseconds. Similarly, we also observed the rate-dependent ATP efficacy profile, with the highest efficacy at ACL of 400-449 ms (figure 4).

6.4.4. Implication in device programming

In patients with recurrent AF post AF ablation, utilization of MVP, APP and aATP therapy should be considered given the fact that patients were benefitted from these algorithms. Detection of atrial tachyarrhythmia episodes that occurs in regular pattern as well as higher ACL (especially the zone of 400-449 ms) could help in identifying organized AT/AFl episodes, so that these therapies will results in a greater benefit in these subsets of patients. In patients with clinically documented AF, aATP could also be considered because transitions between AF and organized atrial tachyarrhythmias are observed frequently. More aggressive aATP therapies can be considered in some patients with low aATP efficacy, but evident episodes of AT or flutter. MinVP showed an excellent benefit in extending battery longevity, at around 1.8 years.[250] However, considering atrial pacing therapy algorithms may impact pulse generator longevity, the therapy should be inactivated if efficacy remains low over the long term.

6.4.5. Study limitation

Our study has several limitations. The number of patients included in this pilot study have been limited, which precludes definite conclusions. Nevertheless, it might be implemented to generate hypotheses. Also, this study was performed in a single centre, and given all patients

have had both procedures (pacemaker implant and AF ablation) prior to enrolment with varied numbers of procedure and time frame from the procedures until the recruitment date, these may affect AF burden of each subject. However, with the cross-over design, this bias might potentially be reduced. In addition, AF burden is not normally distributed, which has a negative impact on statistical power and the disadvantages of non-parametric analyses. No washout period between the observation periods in this cross-over study design, which may result in the possible ongoing effects of atrial remodelling from period after randomisation and impairing the outcome of the patients in cross-over period.

6.5. Conclusion

The present pilot study suggests that in the subset of patients who had AF ablation, atrial pacing therapies is significantly associated with 40% reduction in AF events. Furthermore, it is also shown that aATP efficacy is significantly higher in AT/AF events with longer ACL. Further study will be required to identify the specific subset of patients who will gain an additional value with the addition of preventative and termination pacing to the therapies.

6.6. Tables

Table 1. Programming parameter at randomization

Parameter	Control group N=47	Intervention group N=43
Detection		
AF Interval	200	200
AT interval	200-300	200-300
Minimized ventricular pacing (AAI to DDD)	ON	ON
Atrial Preventative pacing	OFF	
- Atrial rate stabilization		
• Increment (%)		25
• Minimum pacing interval (ms)		95
- Post mode-switch overdrive pacing		
• Overdrive rate (bpm)		80
• Overdrive period (minutes)		5
- Atrial preference pacing		
• Decrement (ms)		50
• Search beat		10
Atrial anti-tachycardia pacing	OFF	
- ATP therapy 1		Ramp
- ATP therapy 2		Ramp
- ATP therapy 3		Burst+
Episode duration before aATP (minutes)		0
Rhythm based re-arming		ON
Time to stop therapy (hours)		72

Table 2. Baseline characteristics

Variables	N=54
Age (mean ± SD)	71.8 ± 6.8
Female (n, %)	20 (37.0)
Body mass index (mean ± SD)	28.5 ± 4.1
Type of AF - Paroxysmal (n, %) - Persistent (n, %)	 31 (83.8) 6 (16.2)
Comorbidities	
Hypertension (n, %)	41 (75.9)
Diabetes Mellitus (n, %)	11 (20.8)
Hyperlipidemia (n, %)	20 (37.0)
Obstructive sleep apnea (OSA) (n, %)	17 (32.1)
Chronic obstructive pulmonary disease (n, %)	1 (1.9)
Stroke/transient ischemic attack (n,%)	3 (5.6)
Coronary artery disease (n, %)	7 (13.0)
Coronary bypass surgery (n, %)	3 (5.6)
Other medication	
Calcium channel blocker (n, %)	11 (20.8)
Angiotensin receptor blocker (n, %)	22 (41.5)
ACE inhibitor (n, %)	11 (20.8)
Beta blocker (n, %)	21 (39.6)
Amiodarone (n, %)	0 (0)
Digoxin (n, %)	0 (0)
Flecainide (n, %)	14 (25.9)
Sotalol (n, %)	6 (11.1)
Echocardiogram parameters at baseline	
LV ejection fraction - % (mean ± SD)	65.9 ± 8.1
Left atrial volume index - (mean ± SD)	28.0 ± 6.1
Left ventricular end diastolic diameter – mm (mean ± SD)	40.4 ± 16.3
Left ventricular end systolic diameter – mm (mean ± SD)	19.6 ± 14.4
Valves - Severe mitral regurgitation (n, %) - Severe aortic regurgitation (n, %) - Severe mitral stenosis (n, %) - Severe aortic stenosis (n, %)	 0 (0) 0 (0) 0 (0) 0 (0)

6.7. Figures

Figure 1. Incidence of short-term major complication based on type of procedure

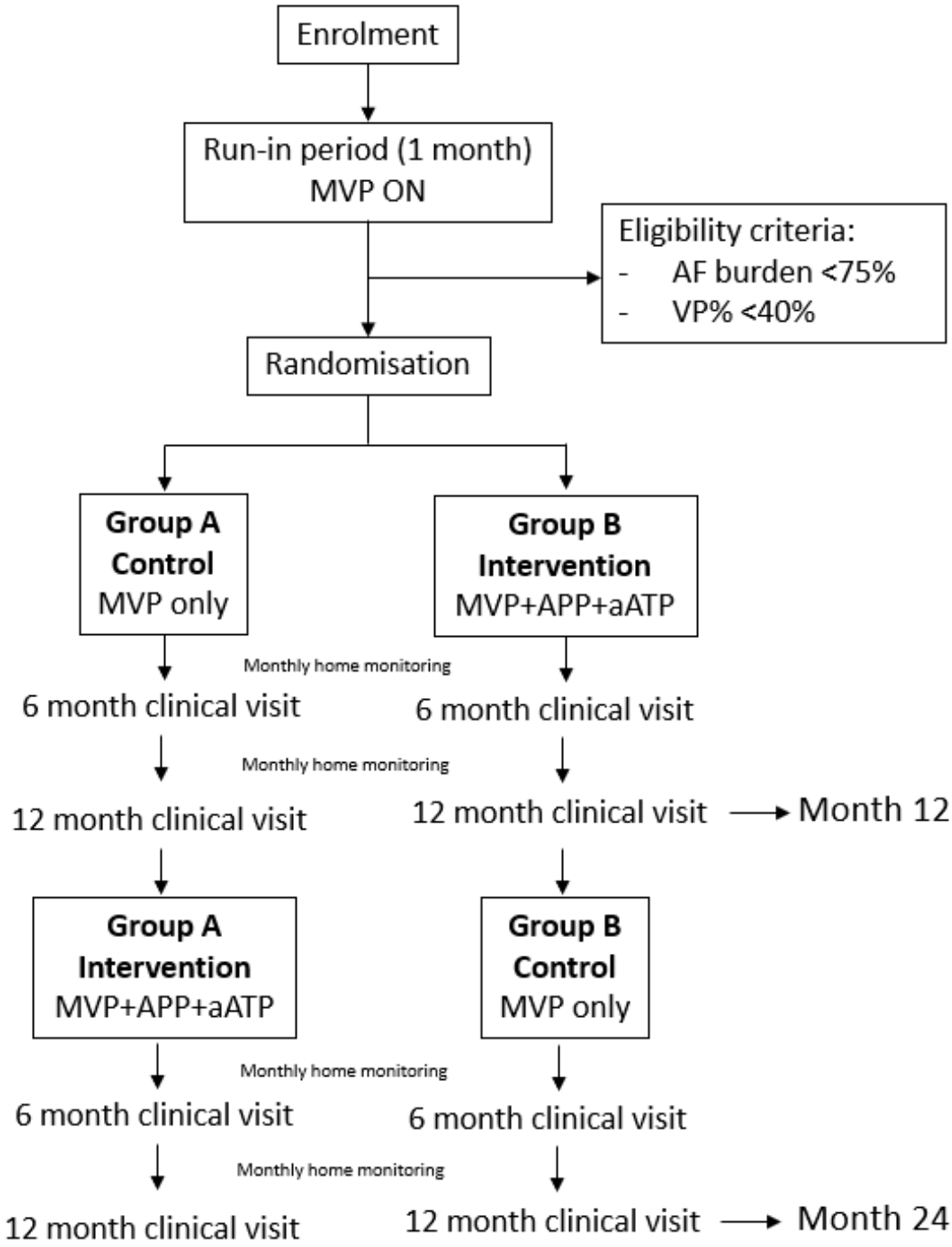


Figure 2. Baseline data. (a) Significant difference between AP% in intervention vs control group. No significant difference of VP% between both groups.

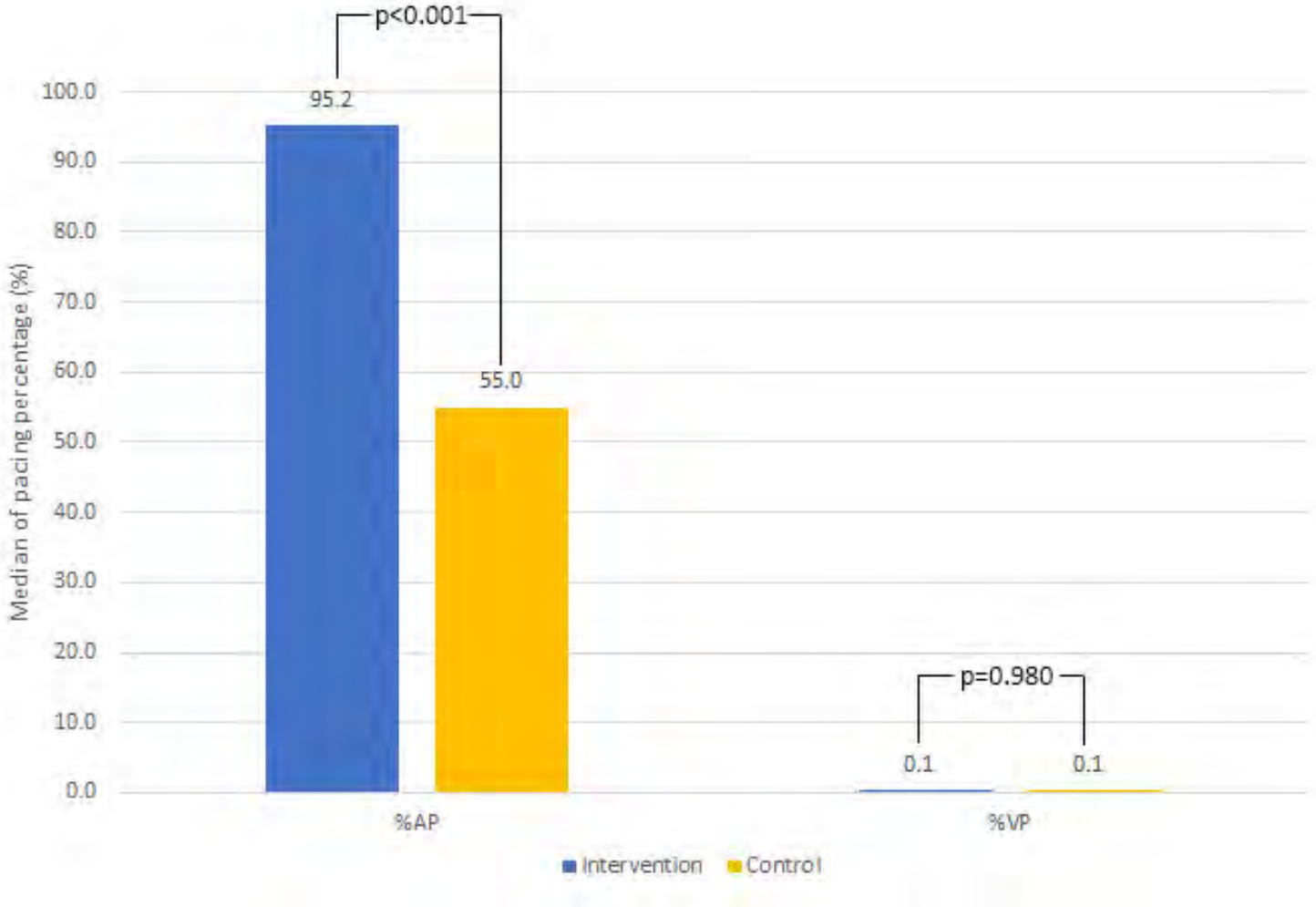


Figure 3. Multivariate analysis of outcome of AF events

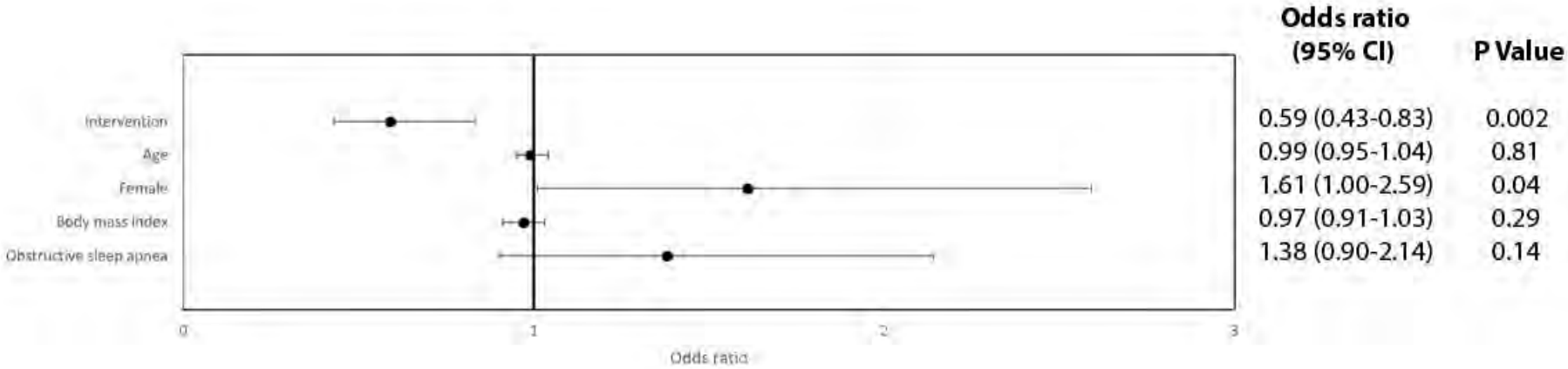
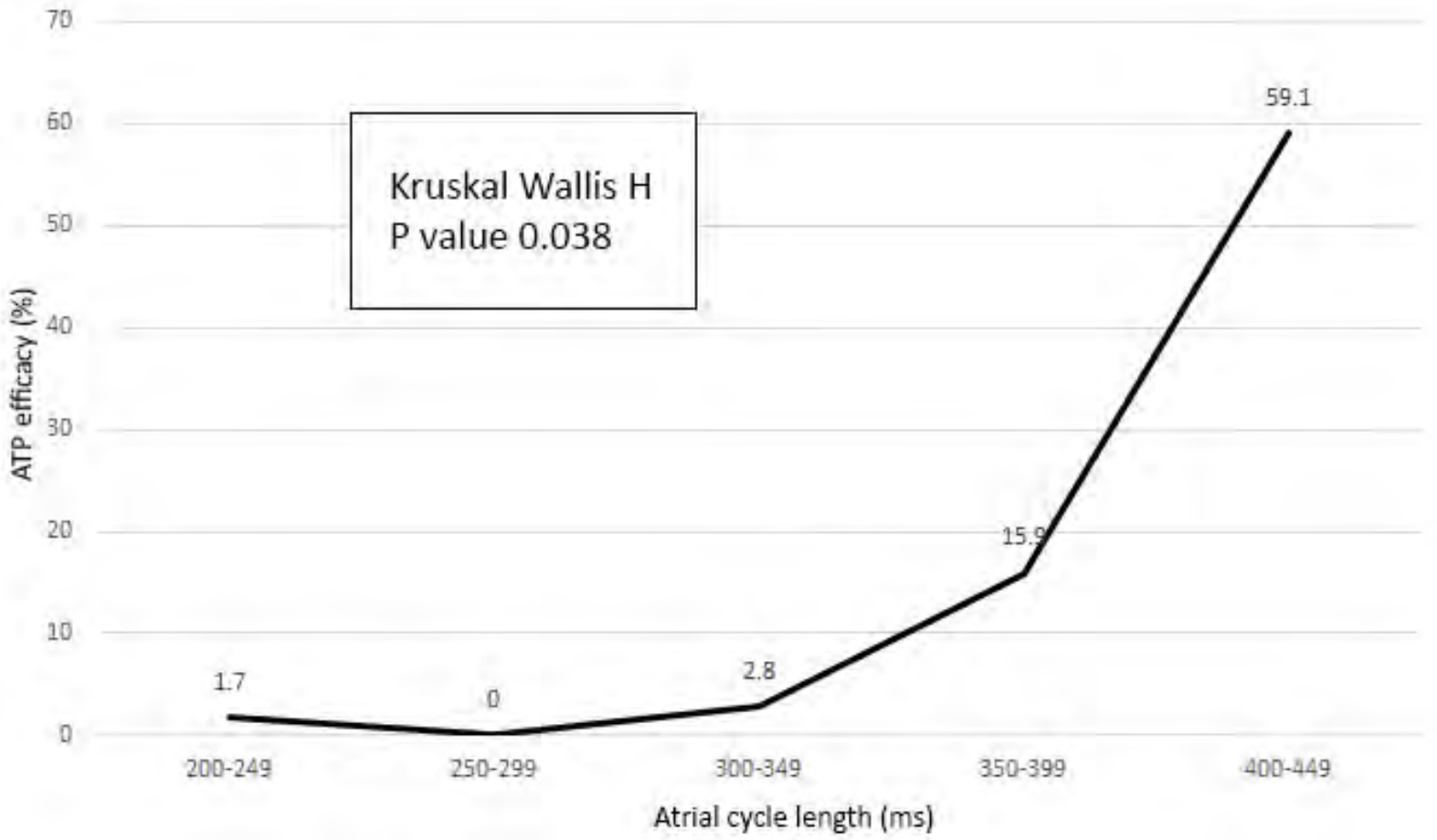


Figure 4. Percentage of ATP efficacy based on atrial tachyarrhythmia cycle length. Data is shown in median and interquartile range.



CHAPTER 7

Magnetic Resonance Imaging in Non-Conditional Pacemakers and Implantable Cardioverter-defibrillators: A Systematic Review and Meta-analysis

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7.1. Introduction

The use of cardiac implantable electronic devices (CIEDs) is on the rise due to prolonged life expectancy and the expanding indications for CIEDs implantation. It has been estimated that the need for a magnetic resonance imaging (MRI) scan within one year of device implantation and over the lifetime of the patient with CIED is around 10 and 75% respectively.[251] With the recent development of MRI-conditional CIEDs, MRI scanning in patients with MRI-conditional CIEDs is increasingly being performed. However, a recent population-based cohort study showed that around 90% of all CIEDs in current use are non-conditional in the MRI environment.[252] Traditionally, MRI has been considered contraindicated in the CIED population, due to safety concerns relating to the exposure to static and gradient magnetic fields as well as radiofrequency energy. As a result, patients with older generation non-conditional CIEDs are likely to be denied access to MRI scans in many centres.

There is growing evidence that MRI scanning in patients with non-conditional CIEDs can be performed safely without patient harm or clinically significant changes in CIEDs parameters with appropriate device programming, patient screening and monitoring.[253] To this end, the 2017 Heart Rhythm Society expert consensus statement provided a Class IIa recommendation (level of evidence B) for MRI scanning of non-conditional CIEDs.[135] More recently, the evidence base for the safety of MRI scanning in non-conditional CIEDs has grown significantly with additional data from almost 2000 patients.[254-256] Here, we performed an updated systematic review and meta-analysis to evaluate the safety of MRI scanning in patients with non-conditional CIEDs.

7.2. Methods

7.2.1. Literature search and data sources

This meta-analysis was registered on PROSPERO (CRD42019118485) and conducted in accordance with the MOOSE guidelines (*Supplementary table 1*). Searches were conducted using the medical scientific electronic databases: PUBMED, EMBASE, and CINAHL from inception to 5th December 2018 to identify all relevant studies. The search used keywords of 'magnetic resonance imaging' AND 'pacemaker' OR 'implantable cardioverter defibrillator' OR 'cardiac resynchronization therapy'. The search was limited to the articles in English language and human studies. All references obtained through the databases were reviewed manually. Bibliographies of retrieved articles and reviews were searched manually for additional publications.

7.2.2. Study selection and quality assessment

Citations were included if the following criteria were met: (i) Enrolment of patients with non-conditional CIEDs undergoing MRI scanning; (ii) adverse events during or immediately after MRI scanning were assessed. Studies were excluded if the MRI conditionality of the CIEDs was undisclosed or if they included <10 patients or if they were review/case reports/series. Eligibility assessment was performed independently by two investigators (DAM, JEZC). Disagreements were resolved by consensus. Selected publications were analyzed for the following outcomes: [A] Adverse events relating to MRI scans, comprising of: (i) death; (ii) peri-procedural symptoms – including heating or torque at generator site, chest pain, or palpitation (iii) electrical reset – defined as reversion to manufacturer's specified parameters (indicated as Safety Mode, Reset Parameters, or Back-Up mode) (iv) lead failure – defined as failure of lead function requiring replacement or revision; (v) generator failure – defined as inability to communicate with CIEDs via device programmer or sudden drop in battery voltage

requiring replacement; (vi) inappropriate pacing; [B] Changes in CIEDs parameters, comprising of: (i) pacing lead threshold increase (≥0.5 V, ≥1.0 V, or ≥50%); (ii) amplitude decrease (≥ 50% for P wave and ≥25% and ≥50% for R wave); (iii) pacing lead impedance increase (≥ 50% or ≥50Ω) (iv) battery voltage decrease (>0.04 V).

Data extraction sheet was developed based on Cochrane Consumers and Communication Review Group's data extraction template and refined accordingly. Assessment of the methodological quality of clinical trials included was performed according to the Cochrane Collaboration's tool for assessing risk of bias. The relevant checklists are included in the supplementary material.

7.2.3. Statistical analysis

This meta-analysis was carried out utilizing the StatsDirect Statistical software (Version 3.1.21, StatsDirect Ltd, Cambridge, UK). For nominal values, the pooled weighted proportion was used with its 95% confidence interval (CI). The Mantel-Haenszel fixed effect and the Der Simonian–Laird random effect models were followed when heterogeneity was found among studies by means of I^2 and the statistical Cochran's Q tests. I^2 values of <25%, 25–50 and >50% normally correspond to small, medium and large heterogeneity, respectively. Statistical significance was defined as $P<0.05$.

7.3. Results

A total of 4,609 English citations were identified using the search strategy. After removing duplication, 3,114 studies were screened based on the title and abstract. 2,836 studies were excluded on account of relevance (Figure 1). After secondary review of the full-text articles in the remaining 278 selected studies, 204 studies were excluded because they were review

articles, case reports or case series, cohort studies or conference abstracts. A total of 39 studies were excluded due to repetitive publication (n=4), not including non-conditional devices (n=31) and undisclosed conditionality of the CIEDs (n=4). As a result, 35 cohort studies (supplementary table 2) with a total of 5,625 patients and 7,196 MRI scans (0.5-3 Tesla[T]) in non-conditional CIEDs were included in the analysis (Table 1).

Of the 35 included studies, 31 studies (n=5,518) utilized 1.5T MRI, 3 studies (n=78) utilized >1.5T MRI and 1 study utilized both 1.5 or 3T MRI (n=29).[257] 10 studies recruited pacemaker-dependent patients (n=561), in which 2 of these patients had 3T MRI. There was a total of 2,622 atrial pacing leads, 3,124 right ventricular pacing leads, 289 left ventricular pacing leads and 1,851 defibrillator leads. None of the patients with abandoned (n=26) or epicardial leads (n=8) had 3T MRI. Majority of the MRI scans were for head & neck (39%), spinal (17%) and abdomen/pelvis regions (12%). The details of the study design are provided in Table 2.

7.3.1. Adverse events relating to MRI scans

Figure 2 demonstrates the pooled proportion of peri-procedural events.

7.3.1.1 Death

MRI scan-related mortality was reported in 9 studies (n=2,122 patients). These studies showed no death occurred during or immediately after the procedure.

7.3.1.2 Symptom of heating or torque

Symptom associated with either torque or heating of the generator or lead, chest pain, or palpitation, induced by MRI were described in 25 studies (n=4,531 patients). The overall analysis shows that the incidence was very low at 0.71% (95% CI 0.35%-1.18%).

7.3.1.3 Electrical reset

Of 25 studies (n=4,896 patients), electrical resets occurred in 76 patients with 83 MRI scans, yielding the absolute incidence of 1.43% (95% CI 0.64-2.54). Notably, in the studies disclosing the details of these devices, all resets occurred in older generation CIEDs that were first released in the market before 2005 (Supplementary Table 5).

7.3.1.4 Lead and generator failure

Fifteen studies (3,995 patients) examined the outcome of lead or generator failure. Of these, there were no cases of non-conditional lead failure reported. Additionally, two cases of generator failure were reported in two studies, with pooled absolute incidence of 0.14% (95% CI 0.05%-0.28%). In one study, the implantable cardioverter-defibrillator (ICD) generator could not be interrogated during post-MRI evaluation. However, it was reported that anti-tachycardia therapy was left in the active mode during MRI, therefore multiple anti-tachycardia pacing therapy attempts due to false ventricular fibrillation detection were notable in this particular case.[258] The other study showed battery longevity < 1 month following an electrical reset, which resulted in the inability to change mode due to battery status.[254] Both devices were immediately replaced.

7.3.1.5 Inappropriate pacing

A total of 2,772 patients were included in 16 studies reporting the outcome of inappropriate pacing. This analysis showed an incidence of 0.37% (95% CI 0.09-0.53). Most cases demonstrated a decrease in heart rate temporarily during MRI procedure due to pacing inhibition, except in one case, the pacing rate was increased to magnet rate (Guidant Insignia).

7.3.1.6 ICD shocks

No inappropriate ICD shocks occurred during MRI scans of non-conditional ICDs (10 studies, n=911 patients). In these studies, tachyarrhythmia therapies including anti-tachycardia pacing and shocks, were deactivated before the MRI scans.

7.3.2. Changes in CIED parameters

The pooled proportion of patients who had changes in the CIED parameters before and after MRI scans were analysed (Figure 3).

7.3.2.1.Lead threshold

Twelve studies with a total of 7,987 leads in 3,604 patients reported the incidence of increased pacing threshold. Pooled analysis was performed in the group of studies stratified by an absolute increase of ≥ 0.5V (6 studies), ≥ 1.0V (4 studies), or ≥ 50% (2 studies). A significant increase in pacing threshold was observed in 1.1% (95% CI 0.7- 1.8%; I^2 34.5%), 1.0% (95% CI 0.1-2.9%; I^2 69.3%) and 1.1% (95% CI 0.2-2.8%; I^2 81.6%) respectively.

7.3.2.2.Lead Impedance

Eight studies (n=3,284 patients, 7,713 leads) analyzed the change of lead impedance. The incidence of impedance changes >50Ω (5 studies) and >50% (3 studies) in low voltage devices

was 4.8% (95% CI 3.3% – 6.4%; I^2 62.9%) and 0% respectively. There were 132 of 727 scans (n=658 patients) with high-voltage lead impedance change of >3Ω (22.4%, 95% CI 13.7-32.5%; I^2 70.5%).

7.3.2.3.P and R wave sensing

The incidence of decreased P and R wave amplitudes of ≥50% were reported in six (n=3,274 patients, 2,883 leads) and five studies (n=3,165 patients, 3,515 leads) respectively. The pooled incidence of the decrease in P wave and R wave sensing were 1.5% (95% CI 0.6-2.9%; I^2 77.5%) and 0.4% (95%CI 0.06%-1.1%; I^2 74.4%) respectively.

7.3.2.4.Battery voltage

Five studies (n=1,453 patients) evaluated the incidence of battery voltage drop of >0.04V, with an incidence of 2.2% (95% CI 0.2%-6.1%; I^2 90.3%).

7.3.3. Risk of bias within studies

The risk of bias assessment in the included studies is shown in Supplementary Table 5. All the studies included cohorts with appropriate study methodology and minimum risk of bias. No study was excluded based on study quality.

7.4. Discussions

The key finding from this systematic review and meta-analysis of 5,625 patients with non-conditional CIEDs who underwent 7,196 MRI scans is that low incidence of adverse events and changes in permanent pacing or ICD leads parameter with no cases of inappropriate ICD shocks or death reported. In addition, electrical reset was the most common adverse event (1.43%), occurring exclusively in older generation devices (pre-2005).

Of note, the evidence for MRI safety in patients with non-conditional CIEDs was derived primarily from scanners of ≤1.5T. Of all 35 studies, only 4 studies performed MRI with 2T and 3T machines. It remains unknown whether higher Tesla MRI scans will translate into higher theoretical risks of adverse events. Interestingly, evidence from ex-vivo experiments showed less temperature increase with 3T as compared to 1.5T MRI scans.[259]

7.4.1. Potential hazards of MRI environment to CIEDs

MRI scans are traditionally contraindicated in patients with CIEDs due to initial reports of deaths when appropriate screening, reprogramming and monitoring were not in place.[136] Theoretical safety issues could include the following: First, the radiofrequency fields in the MRI environment can produce high currents to result in the heating of the CIEDs' lead tip and injury of the surrounding myocardial tissue, leading to increases in pacing threshold and impedance.[137] Second, there is a potential of myocardial stimulation leading to triggering of dangerous arrhythmias, inappropriate tachycardia or inappropriate pacing inhibition. While tachyarrhythmia therapy delivery during MRI is not likely to occur because of saturation in the magnetic field, permanent device failure might still happen after a given number of unsuccessful attempts to charge capacitor.[140] Third, CIEDs can be susceptible to magnetic force and torque exerted by the static field of the MRI scanner, resulting in pulling or torque sensation without clinical consequences.[141] Fourth, older generation CIEDs have magnet-activated reed switch that is aimed at preventing any interference during electrocautery surgery. However, when reed switch is activated, asynchronous pacing occurs at magnet rate and tachycardia therapy is disabled with potential risk for untreated tachyarrhythmias as well as accelerated battery depletion. Last, there is a risk of electrical reset of CIEDs in the MRI environment that reverts all programming to factory default settings.

MRI-conditional CIEDs was specifically designed to ameliorate the adverse interaction between MRI and pacing system, including modifications of the lead to reduce RF heating, internal circuitry to reduce potential inappropriate cardiac stimulation, limiting the amount of ferromagnetic materials, reducing disruption of internal power supply by a robust fron-end protection network and hybrid filtering, replacing the reed switch, and dedicated programming pathway during MRI. These modifications demonstrated to be effective and safe without showing any potential hazards related to 1.5 T MRI environment.[260] Similar to that, this updated meta-analysis of MRI scanning in non-conditional CIEDs demonstrates very low incidence of adverse events with no cases of inappropriate ICD shocks and death. Specifically, an increase of 3Ω in high-voltage lead impedance is not clinically significant given that lead fractures were highly suspected only with abrupt impedance increase of >75% or >100Ω.[138] Notably, all the included studies disclosed strict programming and monitoring protocol during the MRI scanning procedure. In general, CIEDs were programmed into asynchronous pacing, particularly in studies enrolling pacemaker dependent patients, or monitor only for non-pacemaker dependent patients. Tachyarrhythmia therapies, including anti-tachycardia pacing and shocks, were turned off during MRI scans. MRI procedures were supervised by either cardiologists or cardiac nurses who were trained in advanced cardiac life support and cardiac technicians with experience in device programming. Patient monitoring included the minimum of electrocardiogram and pulse oximetry.

7.4.2. Current practice of MRI scans in patients with CIEDs

Despite the availability of MRI-conditional devices and increasing evidence in the safety of MRI in non-conditional CIEDs, access for MRI scan in patients with CIEDs remains difficult. A population-based study reported that in almost 17,000 patients with CIEDs, only 0.3% of patients had MRI.[252] In addition, it is also shown that MRI utilization is lower in ICD patients

compared to non-ICD patients despite similar comorbidities.[261] In contrast, in well-prepared MRI centers, emergency MRI scans could also be performed safely in CIEDs patients.[262] Indeed, there are multiple barriers contributing to low rates of MRI uptake in the CIED population. The lack of MRI centres that provide services to CIEDs population might be one of the major reasons.[263] In more equipped MRI centres, real-world practice based on the current radiological guidelines is limited to offering MRI scans to patients with CIEDs that are labelled as MRI-conditional.[264]

It is anticipated that the 2017 HRS expert consensus Class IIa recommendation and the reaffirmed overall safety of MRI scans in patients with non-conditional CIEDs in this updated meta-analysis may change the clinical practice in providing MRI services in non-CIEDs patients. Undoubtedly, the additional measures required to ensure MRI safety such as the expertise to determine clinical risk-benefit and suitability of CIEDs for MRI, to perform pre- and post-scan device programming, to manage any device related adverse events and to arrange future follow-up; may continue to pose significant issues as these are resource intensive and require close coordination between radiology and cardiology services.[263]

7.4.3. Study Limitations

Our study was limited by observational cohort design in all included studies and their inherent potential biases. Several of the studies did not disclose the number of MRI scans based on device conditionality, so that data analysis based on the number of MRI scans could not be performed. In addition, more than half of the studies have small number of participants, which may underestimate the actual incidence of adverse events. Furthermore, significant study heterogeneity was evident in some of the analysis, partly because of the high number of possible combinations between device generator and lead models, MRI scanners with various

field strengths, or different body areas scanned. The nature of the available data precluded differentiation between partial and full electrical reset of CIEDS. Information on the age of the CIEDs leads and the time between leads implants to MRI scanning were unavailable.

7.5. Conclusions

This systematic review and meta-analysis affirm the safety of MRI scanning in patients with non-conditional CIEDs when a strict selection and monitoring protocol is utilized.

7.6. Tables

Table 1: Composite study characteristics by MRI type

	≤1.5 Tesla	**>1.5 Tesla**
Number of studies	32	4
Number of patients	5,541	84
Number of pacemaker-dependent patients	559	2
Number of devices		
- Permanent pacemaker	3,506	75
- Implantable cardioverter-defibrillator	1,845	6
- Implantable loop recorder	9	1
Leads		
- Atrial leads	2,554	68
- Right ventricular leads	3,046	78
- Left ventricular leads	281	1
- Defibrillator leads	1,845	6
- Abandoned leads	26	0
- Epicardial leads	8	0

Table 2: Detailed study characteristics

Study	Year	N	Study design		Procedure details			Age		Gender	
					EP cardiologist	Resuscitation equipment	Others	Mean/median	SD/IQR/ (range)	Male	Female
All CIED (PPM and ICD)											
≤ 1.5T											
Lupo et al[11]	2018	120	Prospective	Single-centre	Y	NM	NM	67	51-76	90	30
Strom et al[13]	2017	123	Prospective	Single-centre	NM	NM	NM	70	19	NM	NM
Higgins et al[36]	2015	198	Prospective	Single-centre	N	NM	ACLS-certified cardiac device nurse; staff radiologist; MRI physicist	66	57-77	216	182
Naehle et al[21]	2011	32	Prospective	Single-centre	NM	NM	NM	60	(23-76)	NM	NM
Cohen et al[16]	2012	109	Retrospective	Single-centre	N	NM	cardiologist with experience in CIEDs	74	11	76	33
Russo et al[6]	2017	1,246	Prospective	Multi-centre	N	Y	physician, nurse practitioner or physician assistant with cardiac device expertise and training in ACLS	73	14	579	420
Do et al[17]	2018	111	Retrospective	Single-centre	NM	NM	ACLS-trained physician/NP/PA	59	14	NM	NM
Samar et al[18]	2017	136	Prospective	Single-centre	Y	Y	EP nurse	NM	NM	NM	NM
Nazarian et al[9]	2017	1,509	Prospective	Multi-centre	RN or EP	NM	RN who had experience in cardiac device programming and training in cardiac life support	69	58-78	961	548
Halshtok et al[37]	2010	18	Prospective	Single-centre	Y	Y	device technicians	59	(11-94)	15	3
Sheldon et al[38]	2015	40	Prospective	Multi-centre	N	Y	pacing nurse, technician, radiologist, and physicist	66	9-24	16	40
Mollerus et al[27]	2008	103	Prospective	Single-centre	Y	Y	NM	NM	NM	NM	NM
Yadava et al[10]	2017	213	Prospective	Single-centre	N	Y	EP nurse or physician assistant with experience in CIEDs functioning and ACLS	63 (PPM), 56 (ICD)	NM	NM	NM
Horwood et al[39]	2016	136	Prospective	Single-centre	NM	NM	device nurse who was trained in ACLS	63	12	117	25
Dandamudi et al[29]	2016	51	Retrospective	Single-centre	Y	Y	NM	59	14	40	18
Camacho et al[31]	2016	14	Retrospective	Single-centre	Y	NM	NM	66	(20-89)	68	36
Hwang et al[12]	2016	29	Retrospective	Single-centre	N	NM	cardiologist	64	(17-83)	20	20
Mason et al[19]	2017	163	Prospective	Single-centre	N	Y	cardiologist and ACLS trained personnel (imaging nurse)	66	(24-93)	102	76
Kaasalainen et al[35]	2014	42	Prospective	Single-centre	N	Y	cardiologist present when MR-unsafe PPM or ICD (later available by phone); radiologist	67	14	37	27
Shah et al et al[34]	2017	89	Prospective	Single-centre	Y for PPM dependent	NM	physician with expertise in device management (typically an EP fellow)	65	N/A	68	37

>1.5 T											
Gimbel et al[25]	2008	14	Prospective	Single-centre	Y	NM	NM	NM	NM	NM	NM
Hwang et al[12]	2016	29	Retrospective	Single-centre	N	NM	cardiologist	64	(17-83)	20	20
PPM only											
≤ 1.5 T											
Sommer et al[20]	2006	82	Prospective	Single-centre	Y	Y	-	67	(4-89)	53	29
Strach et al[23]	2010	114	Prospective	Single-centre	Y	Y	-	59	9	72	42
Vahlhaus et al[15]	2001	32	Prospective	Single-centre	N	Y	cardiologist - for cardiac rhythm analysis and resuscitation	NM	N/A	NM	NM
Sommer et al[14]	2000	44	Prospective	Single-centre	NM	NM	One staff member, adjacent to the patient, provided continuous surveillance during the MR imaging examination	NM	N/A	NM	NM
Martin et al[30]	2004	54	Prospective	Single-centre	Y	Y	-	NM	NM	NM	NM
Naehle et al[43]	2009	47	Retrospective	Single-centre	N	Y	ACLS-trained personnel	NM	N/A	NM	NM
Muehling et al[28]	2014	356	Prospective	Single-centre	N	Y	cardiologist	61	9	229	127
Bertelsen et al[40]	2017	179	Retrospective	Single-centre	N	NM	Cardiac team within 10 minutes	NM	N/A	NM	NM
>1.5 T											
Del Ojo et al[24]	2005	13	Prospective	Single-centre	N	Y	member of research team	70	5.41	10	3
Naehle et al[26]	2008	51	Prospective	Single-centre	Y	Y	NM	66	(10-84)	31	13
ICD only											
≤ 1.5T											
Naehle et al[22]	2009	18	Prospective	Single-centre	Y	Y	NM	62	N/A	NM	NM
Dickfeld et al[42]	2011	22	Prospective	Single-centre	NM	NM	NM	58	15	21	1
Junttila et al[33]	2011	10	Prospective	Single-centre	NM	NM	NM	59	7	9	1
Mesubi et al[32]	2014	31	Prospective	Single-centre	NM	NM	NM	62	13	30	1

ACLS: advanced cardiac life support, CIEDs: cardiac implantable electronic devices, EP: electrophysiologist, ICD: implantable cardioverter-defibrillator, NM: not mentioned, NP: nurse practitioner; PA: physician assistant; PPM: permanent pacemaker, RN: registered nurse.

7.7. Figures

Figure 1. CONSORT diagram showing search methodology

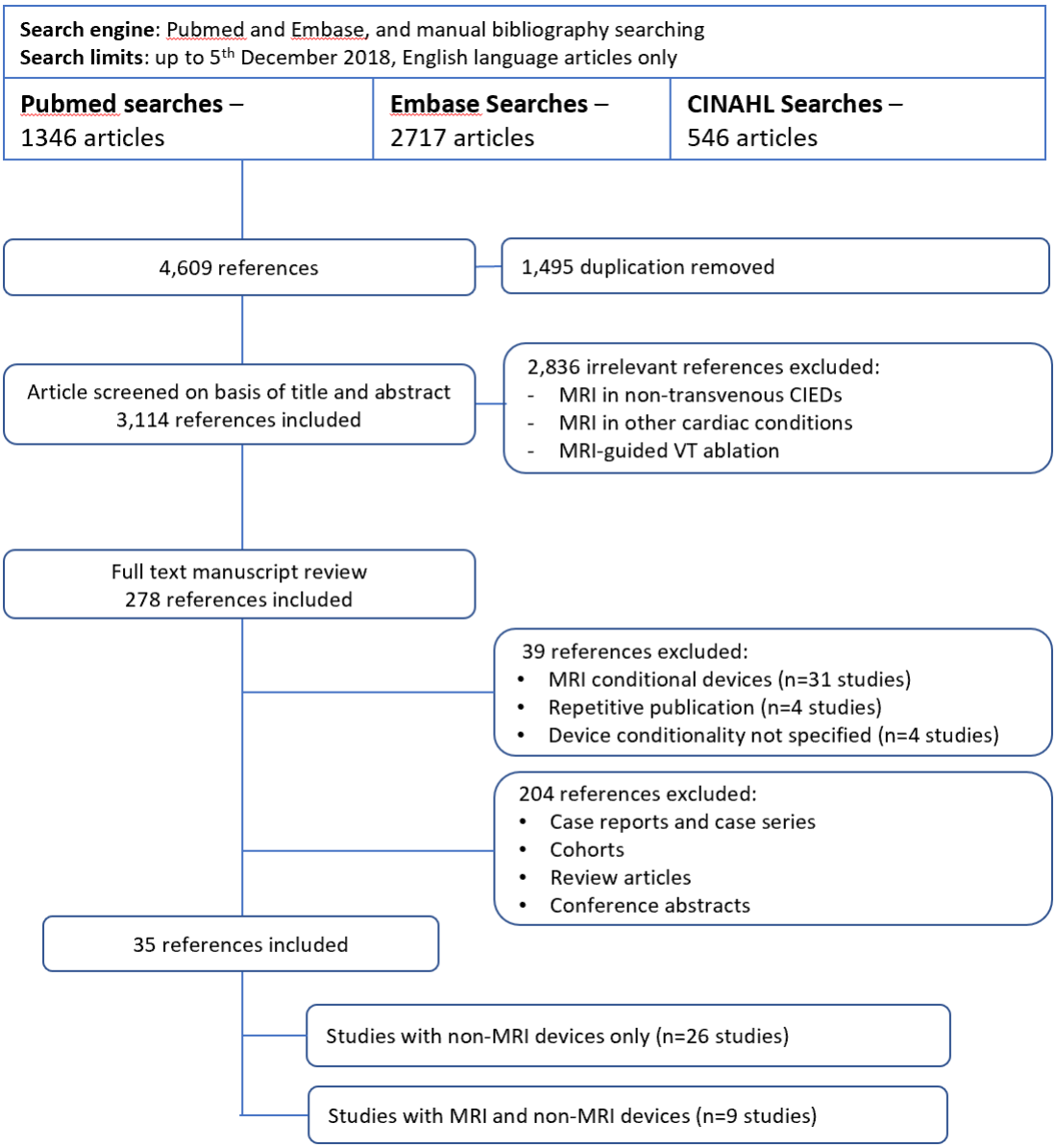
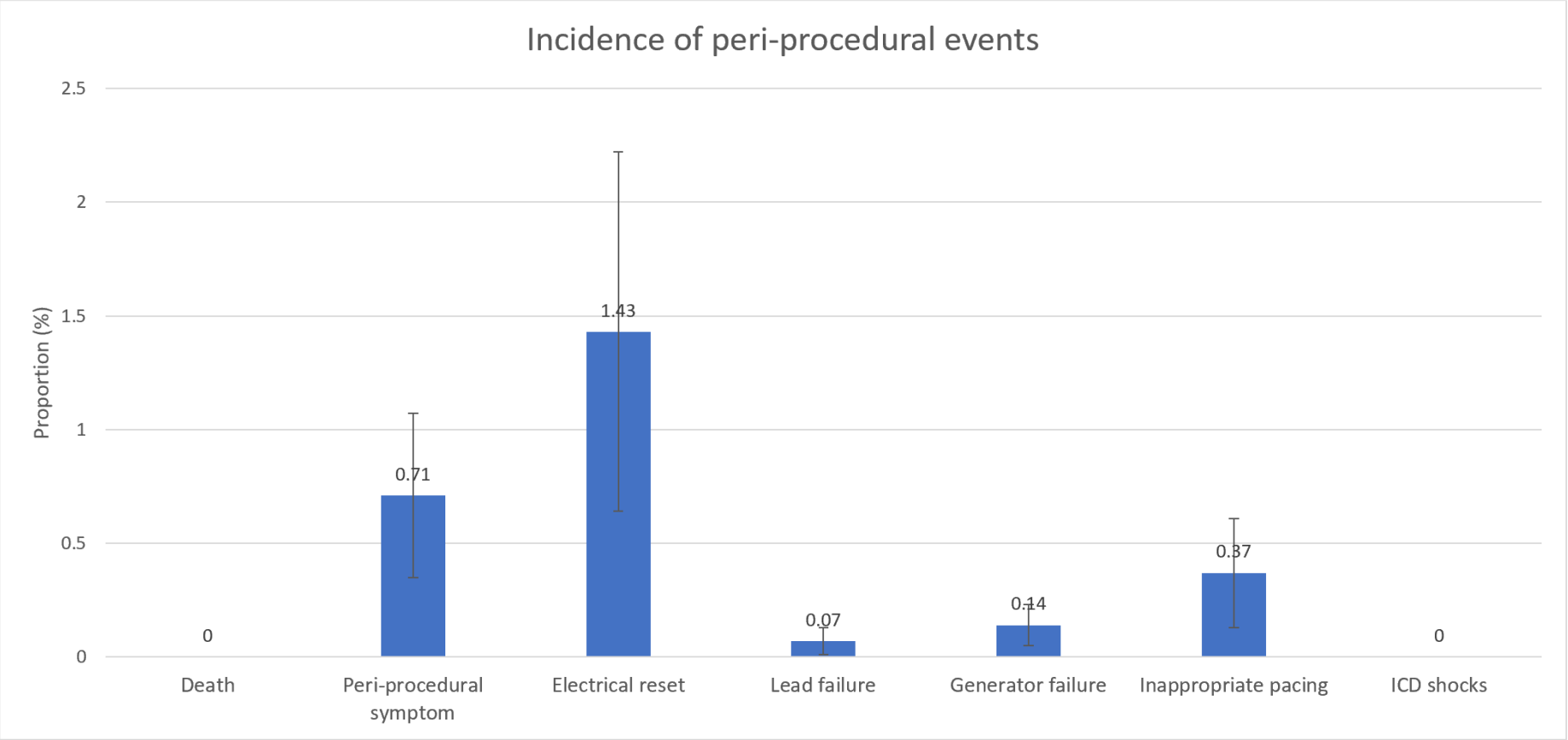
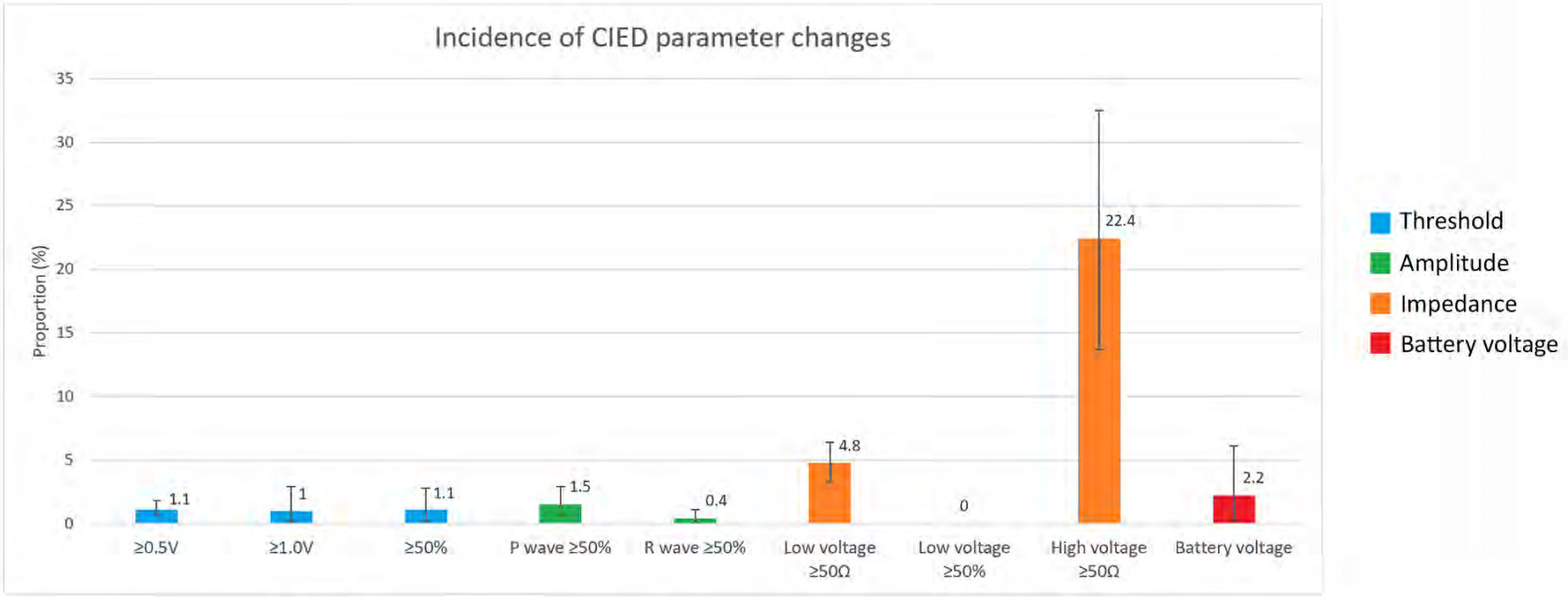


Figure 2. Incidence of MRI-related adverse events



	Death	Peri-procedural symptom	Electrical reset	Lead failure	Generator failure	Inappropriate pacing	ICD shocks
N events	0	19	76	1	2	6	0
N subjects	2,122	4,531	4,896	3,995	3,995	2,772	911
N studies	9	25	25	15	15	16	10

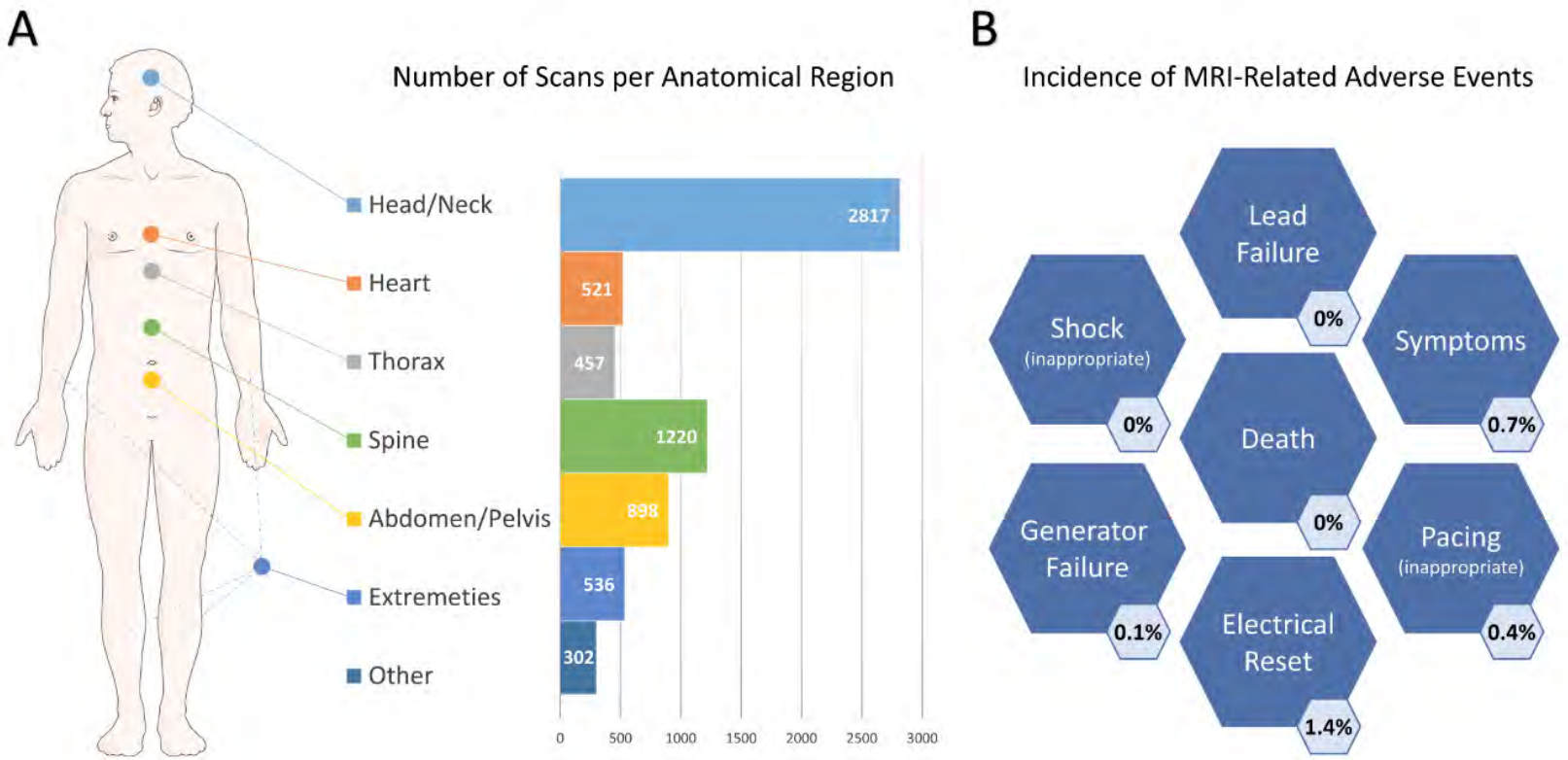
Figure 3. Incidence of CIED parameter changes



	Threshold (atrial and ventricular leads)			Amplitude		Impedance			Battery voltage
				P wave	R wave	Low voltage	Low voltage	High voltage	
Cut-off value	**≥0.5V**	**≥1.0V**	**≥50%**	**≥50%**	**≥50%**	**≥50 Ω**	**≥50%**	**≥3 Ω**	**≥0.04V**
No. of events	32	8	32	35	12	134	0	132	32
No. of leads	3,388	684	3,915	2,883	3,515	3,354	4,359	727 scans	-
No. of subjects	1,577	382	1,645	3,274	3,165	1,476	1,808	658	1,453
No. of studies	6	4	2	6	5	5	3	5	5

Graphical abstract:

A: Numbers of MRI scans per body region. B: Incidence of MRI-related adverse events



CHAPTER 8

Final Discussions and Future Directions

8.1. Final Discussions

Since the first implantation in 1958, cardiac implantable electronic devices (CIEDs) has been one of the successful inventions in modern medicine to manage patients with permanent conduction disease. The benefit of improvement of symptomatic bradycardia and quality of life in the short-term is obvious and well documented. Nevertheless, the deleterious consequences related to long-term effect of pacing have been extensively described in the literatures.

The findings made during this doctoral thesis have provided comprehensive understanding of factors affecting short-term and long-term clinical outcomes of the CIEDs as described in first chapter. These include the understanding of basic electrochemistry of the CIED generator, factors related to acute complication during CIED implantation procedure, clinical outcomes after implants, including development of pulmonary hypertension and utilisation of CIED algorithms in order to provide optimal clinical outcomes of patients with CIEDs, and general consideration of magnetic resonance imaging in patients with CIEDs, particularly in non MRI conditional devices.

Predicted device longevity is an important factor of patient's clinical outcomes in the settings of future need for generator replacements. The second chapter of this thesis relates to understanding of electrochemistry factors of CIEDs in determining CIED longevity. This study also provides the data of the variability of predicted longevity among the different available manufacturers due to unstandardized reporting which may potentially affect physician's clinical judgement. Whilst battery capacity and chemistry as well as housekeeping current are important factors in CIED longevity, these factors are non-modifiable after implants. This

study shows that longevity improvement after implant could be achieved with modification of CIED programming and algorithm that aim at saving battery performance.

Longer-term patient outcomes may also affect by the procedure of CIED implant. Chapter three of this thesis provides information of prevalence of the short-term complication following CIED implants, showing a low rate of complication related to the procedure. Observation from this study have identified that longer procedure time is an independent predictor of complication after CIED implantation procedure. Therefore CIED insertion procedure should aim as efficient in term of procedure duration as possibly performed, without ignoring the safety aspects of the procedure.

The following three chapters concern the clinical outcome and optimisation of CIED including the utilisation of CIED algorithms to reduce the risk of deleterious effects related to CIED implantation. The results from investigation of pulmonary hypertension (PH) development from echocardiographic measurement (chapter 4) after CIED implants gave us the insight of PH as an unrecognised long-term risk following CIED implants. This study also identified the cardiac structural predictors, with right atrial size and mitral regurgitation as the independent predictors of PH development in CIED population. In addition, age is also one of the independent predictors of PF after CIED implants. The meta-analysis (chapter 5) and RCT (chapter 6) of AF prevention algorithms, including minimised ventricular pacing, atrial preventative pacing, and atrial antitachycardia pacing, investigates the strategies to reduce the risk of atrial fibrillation development to optimise patient outcomes. This meta-analysis showed that no significant benefit in the utilization of MVP, APP, and aATP algorithm could be statistically achieved in general CIED with paroxysmal AF population. Nevertheless, in the subset of post AF ablation patients, our pilot study showed a significant reduction in the AT/AF

events. This is likely related to the most common mechanism of AT recurrence after AF ablation that involves gap and trigger macroreentrant AT, which is more responsive to aATP therapy. Unfortunately, the pilot study of the RCT has small numbers of patient samples. Therefore, limited conclusions can be made from these data beyond this.

Whilst being the most important clinical tool for diagnosis in extensive area of clinical practice, magnetic resonance imaging (MRI) has been a major concern in patients with CIEDs due to the risk related to interactions of the magnetic surrounding and the electric devices. Our results in chapter 7 investigates the safety of MRI in patients with CIEDs, especially in non-MRI-conditional devices. This study indicates that the use of MRI in non-MRI conditional is safe, inasmuch as a strict selection and monitoring protocol is utilized.

8.2. Future Directions

The observations made during the course of this thesis have provided important insights into the comprehensive analysis of factors associated with clinical outcomes of patients with CIEDs. However, many questions remain unanswered, some of which are discussed below.

This thesis provides the evidence of sign of PH development from echocardiographic measurement follow-up after CIED implantation. However, despite the accuracy of echocardiogram measure shows high sensitivity and specificity at 85% and 74%, respectively,[265] right heart catheterization is still considered as the gold standard for the final diagnosis of PH based on the current guidelines,[266] which unfortunately could not be gathered in the current study. It would be important to confirm the diagnosis of PH in patients confirmed of having elevated pulmonary pressure from echocardiogram, as well as to further exclude the other possible underlying cause of PH development. In addition to this, the evidence of

transvenous leads in CIEDs as a nidus for thrombus formation has been described,[76-78,267] therefore, the potential causal relationship PH in this subset of patient with lead thrombosis warrants further investigation. Confirmation of PH development in this population will lead to further question whether all patients with transvenous CIEDs would benefit from oral anticoagulation therapy will be interesting to be answered.

Several questions also remain about optimising pacemaker function and algorithm to reduce the deleterious effects of long-term pacing, especially AF. Evolving pacing system and few different options of algorithms have been developed in order to achieve this aim. However, the failure of all these algorithms to significantly decrease the incidence of worsening outcomes in general CIED population showed that a significant amount is yet to be learned of the cellular mechanisms of mechanical and electrical dysfunction associated with persistent pacing. At a clinical level, the subset of some individuals who demonstrated a significant advantage with the utilisation of the algorithm, particularly with AF burden reduction is of considerable importance and remains unexplored. New pacing strategies that offer a more physiologic mode of ventricular pacing such as his bundle pacing or left bundle pacing might be considered as a promising alternative option that warrant further investigation, especially for AF reduction.

Finally, our RCT is a pilot study that investigated the use of AF prevention algorithms, particularly in subset of patients with previous history of AF ablation. In this subset of patients, the evidence showing atrial tachycardia and flutter is more common in the recurrence after AF ablation theoretically suggests that aATP will demonstrate a superior response. However, this pilot study unfortunately had limited number of patients that results in limited conclusion can be made. Further evaluation aATP therapy only in a larger number of patients would warrant

further investigation and be essential for our understanding of this disease and patient management.

CHAPTER 9

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