Complications of leadless vs conventional (lead) artificial pacemakers – a retrospective review

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ABSTRACT
Background: Leadless pacemakers (LPM) are introduced in cardiovascular market with a goal to avoid lead- and pocket-associated complications due to conventional artificial pacemakers (CPM). The comparison of LPM and CPM complications is not well studied at a case by case level.

Methods: Comprehensive literature was searched on multiple databases performed from inception to December 2019 and revealed 204 cases that received LPM with a comparison of CPM. The data of complications were extracted, screened by independent authors and analyzed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.).

Results: The complications of CPM were high in comparison to LPM in terms of electrode dislodgement (56% vs 7% of cases, p-value < .0001), pocket site infection rate (16% vs 3.4%, p-value = 0.02), and a lead fracture rate (8% vs 0%, p-value = 0.04). LPMs had a statistically non-significant two-times high risk of pericardial effusion (8%) compared to CPMs (4%) with a p-value = 0.8.

Conclusion: LPMs appear to have a better safety profile than CPMs. There was a low pocket site and lead-related infections in LPM as compared to CPM. However, LPM can have twice the risk of pericardial effusion than CPMs, but this was not statistically significant.

1. Introduction
In the USA, annually about one million de novo pacemakers are inserted and more than 200,000 pacemakers are replaced [1,2]. Since the invention of the pacemaker in the 1950s, there has been robust evolution in the technology of these devices, such as small battery size with a long half-life, quality, the number of leads, rate and voltage responsiveness. Despite these revolutionary changes, pacemakers face a wide array of complications such as pocket and lead infections, perforation, cardiac tamponade, and pulmonary complications [3,4]. Other long-term complications include lead failure, lead fracture, endocarditis, tricuspid regurgitation, and insulation abnormalities [4,7]. A new type of pacemaker, the leadless pacemaker (LPM), was introduced as an initial concept in animals in the 1970s [8]. Subsequent human studies showed that LPMs have a major complication rate of only 2.7%, major complications are 63% lower than complications with conventional transvenous pacemakers (CPMs) at 12 months follow-up [9]. Further studies substantiated these findings leading to the Food and Drug Administration approval of LPMs in the USA in December 2016 [10]. We sought to determine the safety of these novel pacemakers in our review.

2. Methods

2.1. Search strategy
A literature search for relevant articles was performed from inception to December 2019. We searched PubMed, Ovid (MEDLINE), and the Cochrane Central Register of Controlled Trials using medical subject headings (MeSH) and keywords like ‘Artificial pacemaker,’ ‘Lead pacemaker,’ ‘Wire pacemaker,’ ‘Single chamber pacemaker,’ ‘Dual chamber pacemaker,’ ‘Conventional pacemaker,’ ‘Transvenous pacemaker,’ ‘Cardiac pacing device,’ ‘Cardiac Resynchronization Therapy,’ ‘Permanent leadless cardiac pacemaker,’ ‘Nanostim transcatheter pacing system,’ and ‘Micra transcatheter pacing system.’ The terms from the two subsets were combined in 1:1 combination using Boolean operators, and final results from all the possible combinations were downloaded into an EndNote library. A thorough
search through the reference list of the articles published. The full search strategy is shown in the PRISMA diagram (Figure 1), and supplemental table 1.

2.2. Study selection and selection criteria

Cases reporting CPM- or LPM-related complications were selected. The titles and abstracts of the included articles were reviewed independently by three authors (HR, YS, and WU). The studies that met title/abstract screening inclusion criteria were deemed for full-text reading, and subsequent variable of interest was extracted and analyzed.

2.3. Inclusion criteria

Patients with age >18 received pacemaker with any reported indication, cases that used LPM with reported complications, cases with CPM that underwent any complications, and either subsequently got CPM replaced with LPM insertions.

2.4. Exclusion criteria

Patients with age <18, no indication of a pacemaker, and neither CPM nor LPM, no reported complication of CPM, or LPM.

2.5. Statistical analysis

Frequencies of individual complications across the studies were combined and reported. Descriptive analysis of continuous variables was recorded as mean and standard deviation. The comparison between categorical data was performed using Pearson’s chi-squared test. A P value of less than 0.05 was considered significant. The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.)

3. Results

A study population included 204 reported cases. The mean age of patients with CPM and LPM was 71 and 64 years, respectively. The male-to-female ratio was about 2:1 in both CPM and LPM. About 14% of patients had lead pacemaker implantation whereas 86% of patients had LPM implantation. The most frequent overall complication experienced with pacemaker implantation was pericardial effusion in 8% of patients followed by hematoma and perforation in 7% of patients.

We stratified the complications based on the type of pacemaker and found that electrode dislodgement was seen significantly higher in CPM group (CPM vs LPM: 56% vs 7%, p-value = 0.00). Site infection was higher in CPM (pocket site = 16% of cases, p-value = 0.02) in CPM, whereas LPM had lower site infection (right ventricular site infection = 3.4% of cases (patients),

Figure 1. Preferred reporting items for systematic review and meta-analysis (PRISMA) flow diagram showing search strategy.
CPMs had a significantly 8% higher incidence of lead fracture as compared to LPM with a p-value = 0.04. There was no significant difference seen between CPM and LPM for complications such as pericardial effusion (8% vs 4%, p-value = 0.8), hematoma (8% vs 7.4%, p-value = 0.58), and thrombosis (4% vs 4%, p-value = 0.66). A detailed comparison of the complications is given in supplemental table 2. The combined complications of any artificial pacemaker including lead and leadless in our patient population are shown in bar chart below in Figure 2. The percentage complications of conventional (lead) pacemakers and leadless pacemakers are shown in Figures 3 and 4.

4. Discussions

The CPM includes single-chamber, dual-chamber pacemakers, biventricular, and rate-responsive pacemakers [1]. Currently, there are two LPMs available, including a Micra transcatheter Pacing system (Medtronic, Dublin, Ireland) and the Nanostim Leadless Cardiac Pacemaker (St. Jude Medical, St. Paul, MN). LPMs are inserted percutaneously via a catheter-guided femoral vein approach. Both Medtronic and St. Jude Medical LPMs differ in size, proximity to the myocardium, and responsiveness [11]. LPMs are implanted in the right ventricle directly for sensing and pacing; therefore, they are believed to decrease the risk of lead-associated infection but can have potentially higher risks of perforation and cardiac tamponade. Complications associated with any artificial pacemaker are shown above in Figure 2. CPM had a higher proportion of lead fracture, lead infection, and site in comparison to LPM. The risk of other minor complications was comparable between the two groups and included perforation (4% vs 7.4%, P-value = .45), surgical revision (4% vs 4.6%, p-value = 0.68), mitral regurgitation (0% vs 1.1%, p-value = .76). The detailed comparison data of complications between LPM and CPM are shown above in Figures 3 and 4.

Our findings were consistent with previously reported studies stating better efficacy and safety of LPMs are promising. The results of the Micra study found that LPM has a 48% lower complication rate, 47% fewer annual hospitalizations, and 82% lower pacemaker re-insertion rate compared to CPM [12]. Our results endorse not only previous findings but also highlight rare LPM-associated complications.

The complications of pacemakers can be broadly classified into the lead, pulse generator, arrhythmic, and miscellaneous complications.

4.1. Lead complications

The complications of CPMs include lead infection, lead failure, lead fracture, lead dislodgement, tricuspid regurgitation, increased defibrillator threshold, endocarditis, and sepsis. The cardiac mortality due to CPM can be associated with 31% of deaths [5,13]. Lead complications due to CPMs also include lead noise or loss of insulation. The lead can be extracted using mechanical snares or laser technology; this has been associated with injury to the vessels or endocardium [14,15].

The FOLLOWPACE study and Danish registry reported the rate of lead dislodgement in CPMs and LPMs to be 3.3% and 1.2%, respectively [16]. The LEADLESS II trial showed similar results including device dislodgement (1.7%), cardiac perforation (1.3%), and higher pacing thresholds requiring device
repositioning (1.3%). These results are consistent with our review showing a higher rate of lead fracture and infections. Also, lead dislodgment rate was negligible in LPMs compared to CPMs. Valvular complications secondary to lead impaction on the tricuspid valve or the direct impact of the LPM were also reported in both groups, but these complications were not significantly different between the two groups (LPM 0% vs CPM 1.1%, \( P = .76 \)).

### 4.2. Generator complications

Pulse generator complications are uncommon and account for less than 2% of the complications [17]. Generator complications can be peri-procedural including hematoma, infection of the pocket, device dislodgement, cardiac perforation, pericardial effusion, and cardiac tamponade [18]. In CPMs, a subcutaneous pocket at the site of the device is the source of local infection, erosion, and bacteremia in 1% to 2% of cases [19,21]. LPMs are associated with low rates of infection in general due to the absence of a subcutaneous pocket and the small surface area of LPMs. Infection associated with LPMs can be procedurally related including abdominal wall infection, infected groin hematoma, and sepsis [9]. In our study, both the CPMs and LPM have almost the same percentage of peri-procedural hematoma formation (8% vs 7.4%, \( P\)-value = 0.58). In the LEADLESS II trial, 6.5% of the 526 patients were reported to have a hematoma due to cardiac perforation, and 1.3% of that 6.5% subgroup had pacemakers implanted in the ventricle through right ventricular sensing and pacing [22]. Another prospective study named Micra investigational device exemption (IDE) had 719 pacemaker implants and reported cardiac perforation in 1.5% of the cases [23]. In our study, we found a higher but statistically insignificant pericardial effusion risk with LPMs of 8% (\( p\)-value = 0.05) compared to CPMs at 4.2% [24]. In the LEADLESS trial, at a one-year follow-up, the Nanostim device was shown to have stable pacemaker electricity, rate responsiveness, and without any device-related complications [25]. Overall, our analysis showed no significant difference in the CPM- and LPM-associated generator complications (8% vs 2.3%, \( p\)-value = 0.16) or threshold/electromagnetic complication (0% vs 2.8%, \( p\)-value = 0.51), respectively.

### 4.3. Miscellaneous

Rare complications secondary to pacemakers can include heart failure, pulmonary oedema, pericardial effusion, venous thrombo-embolism/deep venous thrombosis (DVT), pulmonary embolism, lymphatic
5. Conclusions
The goal of the study was to compare the difference of complications of CPM vs LPM by reviewing the relevant literature in available databases. Our results showed that LPM significantly reduces the risk of lead-associated complications, such as lead fracture, dislodgement, and infection. However, LPM can have a theoretically higher risk of pericardial effusion, cardiac tamponade, and thrombosis.

Disclosure statement
No potential conflict of interest was reported by the authors.

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References
[1] Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009—a world society of arrhythmia’s project. Pacing Clin Electrophysiol. 2011 Aug;34(8):1013–1027.
[2] Greenspon AJ, Patel JD, Lau E, et al. Trends in permanent pacemaker implantation in the USA from 1993 to 2009: increasing complexity of patients and procedures. J Am Coll Cardiol. 2012 Oct 16;60 (16):1540–1545.
[3] Ranasinghe I, Parzynski CS, Freeman JV, et al. Long-term risk for device-related complications and reoperations after implantable cardioverter-defibrillator...
implantation: an observational cohort study. Ann Intern Med. 2016 May 3;165:20.

[4] Kirkfeldt RE, Johansen JB, Nohr EA, et al. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur Heart J. 2014 May;35(18):1189–1194.

[5] Tarakji KG, Wazni OM, Harb S, et al. Risk factors for 1-year mortality among patients with cardiac implantable electronic device infection undergoing transvenous lead extraction: the impact of the infection type and the presence of vegetation on survival. Europace. 2014 Oct;16(10):1490–1495.

[6] Polewczyn A, Jache W, Tomaszewski A, et al. Lead-related infective endocarditis: factors influencing early and long-term survival in patients undergoing transvenous lead extraction. Heart Rhythm. 2017 Jan;14(1):43–49.

[7] Udo EO, Zuiithoff NP, van Hemel NM, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm. 2012 May;9(5):728–735.

[8] Spickler JW, Rasor NS, Kezdi P, et al. Totally self-contained intracardiac pacemaker. J Electrocardiol. 1970;3(3–4):325–331.

[9] El-Chami MF, Al-Samadi F, Clementy N, et al. Updated performance of the Micra transcatheter pacemaker in the real-world setting: A comparison to the investigational study and a transvenous historical control. Heart Rhythm. 2018 Dec;15(12):1800–1807.

[10] El-Chami MF, Merchant FM, Leon AR. Leadless Pacemakers. Am J Cardiol. 2017 Jan 1;119(1):145–148.

[11] Bhatia N, El-Chami M. Leadless pacemakers: a contemporary review. J Geriatr Cardiol. 2018 Apr;15(4):249–253.

[12] Duray GZ, Ritter P, El-Chami M, et al. Long-term performance of a transcatheter pacing system: 12-month results from the micra transcatheter pacing study. Heart Rhythm. 2017 May;14(5):702–709.

[13] Brunner MP, Cronin EM, Wazni O, et al. Outcomes of patients requiring emergent surgical or endovascular intervention for catastrophic complications during transvenous lead extraction. Heart Rhythm. 2014 Mar;11(3):419–425.

[14] Hauser RG, Hayes DL, Kallinen LM, et al. Clinical experience with pacemaker pulse generators and transvenous leads: an 8-year prospective multicenter study. Heart Rhythm. 2007 Feb;4(2):154–160.

[15] Buch E, Boyle NG, Belott PH. Pacemaker and defibrillator lead extraction. Circulation. 2011 Mar 22;123(11):e378–80.

[16] Vamos M, Erath JW, Benz AP, et al. Incidence of cardiac perforation with conventional and with leadless pacemaker systems: a systematic review and meta-analysis. J Cardiovasc Electrophysiol. 2017 Mar;28(3):336–346.

[17] Kron J, Herre J, Renfroe EG, et al. Lead- and device-related complications in the antiarrhythmics versus implantable defibrillators trial. Am Heart J. 2001 Jan;141(1):92–98.

[18] Mittal S, Shaw RE, Michel K, et al. Cardiac implantable electronic device infections: incidence, risk factors, and the effect of the AegisRx antibacterial envelope. Heart Rhythm. 2014 Apr;11(4):595–601.

[19] Klug D, Balde M, Pavin D, et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. Circulation. 2007 Sep 18;116(12):1349–1355.

[20] Essebag V, Verma A, Healey JS, et al. Clinically significant pocket hematoma increases long-term risk of device infection: BRUISE CONTROL INFECTION study. J Am Coll Cardiol. 2016 Mar 22;67(11):1300–1308.

[21] Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. N Engl J Med. 2015 Sep;373(12):1125–1135.

[22] Reddy VY, Knops RE, Sperzel J, et al. Permanent leadless cardiac pacing: results of the LEADLESS trial. Circulation. 2014 Apr 8;129(14):1466–1471.

[23] Reynolds D, Duray GZ, Omar R, et al. A leadless intracardiac transcatheter pacing system. N Engl J Med. 2016 Feb 11;374(6):533–541.

[24] Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American college of cardiology foundation/American heart association task force on practice guidelines and the heart rhythm society. J Am Coll Cardiol. 2013 Jan 22;61(3):66–75.

[25] Roberts PR, Clementy N, Al Samadi F, et al. A leadless pacemaker in the real-world setting: the micra transcatheter pacing system post-approval registry. Heart Rhythm. 2017 Sep;14(9):1375–1379.