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Efficacy and safety of leadless pacemaker: A systematic review, pooled analysis and meta-analysis

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ABSTRACT

Background: Leadless pacemakers have been designed as an alternative to transvenous systems which avoid some of the complications associated with transvenous devices. We aim to perform a systematic review of the literature to report the safety and efficacy findings of leadless pacemakers.
Methods: We searched MEDLINE and EMBASE to identify studies reporting the safety, efficacy and outcomes of patients implanted with a leadless pacemaker. The pooled rate of adverse events was determined and random-effects meta-analysis was performed to compare rates of adverse outcomes for leadless compared to transvenous pacemakers.
Results: A total of 18 studies were included with 2496 patients implanted with a leadless pacemaker and success rates range between 95.5 and 100%. The device or procedure related death rate was 0.3% while any complication and pericardial tamponade occurred in 3.1% and 1.4% of patients, respectively. Other complications such as pericardial effusion, device dislodgement, device revision, device malfunction, access site complications and infection occurred in less than 1% of patients. Meta-analysis of four studies suggests that there was no difference in hematoma (RR 0.67 95%CI 0.21–2.18, 3 studies), pericardial effusion (RR 0.59 95%CI 0.15–2.25, 3 studies), device dislocation (RR 0.33 95%CI 0.06–1.74, 3 studies), any complication (RR 0.44 95%CI 0.17–1.09, 4 studies) and death (RR 0.45 95%CI 0.15–1.35, 2 studies) comparing patients who received leadless and transvenous pacemakers.
Conclusion: Leadless pacemakers are safe and effective for patients who have an indication for single chamber ventricular pacing and the findings appear to be comparable to transvenous pacemakers.

1. Introduction

Permanent pacemakers (PPMs) are an established therapy for bradyarrhythmias and heart block. Benefits of pacemaker therapy include symptomatic relief and improved prognosis in certain high-risk groups [1]. A pacemaker system typically consists of a pulse generator situated in a subcutaneous or submuscular pocket connected to one or more leads positioned in the heart via transvenous access [2]. Despite the clear benefit of PPM therapy, previous literature reports significant complications associated with implantation and the long-term use of transvenous devices. Procedure related complications including pneumothorax, cardiac perforation and pericardial effusion have previously been reported in 2.77% of patients within two months of first PPM insertion [3]. Furthermore, lead related complications within two months of implant have been reported in 5.54% of cases, predominantly a result of early lead dislodgement [3]. Long-term follow-up of transvenous leads is associated with an increased incidence of lead insolation break down and lead conductor fracture, resulting in unwanted reintervention and the potential need for lead extraction [4]. Infection is another concern and meta-analysis of prospective studies has found 1.6% infection rate associated with transvenous lead implantation [5]. Transvenous lead-associated endocarditis is a major complication that usually requires extraction, resulting in a mortality rate of 26.9% after 20.1 months of follow up [6]. Pocket

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related complications include haematoma, skin erosion and pocket infection, with clinically significant haematoma being associated with a >7-fold increased risk of infection [7].

The leadless pacemaker has been designed as an alternative to transvenous pacemakers for patients who have an indication for single chamber ventricular pacing and aims to minimise the complications associated with traditional transvenous systems. It consists of an entirely self-contained system which is implanted into the right ventricle via a percutaneous approach. There are two leadless pacemaker systems that have been on the market which are the Micra transcatheter pacing system (Medtronic, Minneapolis, MN, USA) and the Nanostim (St Jude Medical Inc, Saint Paul, MN USA; now Abbott Medical Inc, IL, USA). However, the Micra is currently the only commercially available leadless pacemaker. Initial studies have reported good procedural success rates and relatively low incidence of complications at implantation and during follow-up [8,9] but it is unclear how this compares to real-world data.

We aim to perform a systematic review of the literature to report the safety and efficacy findings of leadless pacemakers and compare these outcomes to patients receiving transvenous pacemakers.

2. Methods

The reporting of this systematic review is in according to the recommendations of the MOOSE checklist [10] (Supplementary Table 1).

2.1. Patient and public involvement

Patients and public were not involved in the conduct of this systematic review.

2.2. Inclusion criteria

We included studies that investigated adult patients who had an indication for single chamber right ventricular pacing and subsequently underwent leadless pacemaker implantation. For inclusion, the studies must have reported the following: implant success rate, procedural characteristics such as procedure duration, fluoroscopy duration, and reposition attempts, outcomes and complications associated with implantation and/or follow-up, and electrical parameters at implant and/or follow-up.

2.3. Search strategy and data extraction

Searches of OVID were conducted using the electronic databases MEDLINE and EMBASE on 13th November 2020 using the following search terms: ("leadless pacemaker" OR "micra" OR "nanostim") AND ("pacemaker"). The search was limited to articles including only human subjects. Included studies were those that investigated adult patients who had an indication for single chamber right ventricular pacing and subsequently underwent leadless pacemaker implantation. For inclusion studies must have reported the following: implant success rate, procedural characteristics such as procedure duration, fluoroscopy duration, and reposition attempts,

Table 1
Study design, patient demographics and patient inclusion criteria.

Study ID	Design; Country; Year	Sample size	Mean age	% Male	Patient inclusion criteria
Bongiorni 2018	Prospective cohort study; Italy; 2014–2017.	52	76	75	Patient were adults with class indication for single chamber ventricular pacing.
Denman 2018	Prospective cohort study; Australia; 2015–2017.	79	78	66	Patients were adults with a class I/II pacing indication Micra transcatheter pacing system implantation.
El Amrani 2019	Prospective cohort study; Spain; 2015.	129	87	57	Patients were adults with Micra transcatheter or transvenous pacing system implantation.
El-Chami 2018	Prospective cohort study; International; 2015–2018.	1817	76	61	Patients were adults with a guideline recommended pacing indication and implanted with Micra.
Haeberlin 2020	Prospective cohort study; Switzerland; 2015–2019.	111	80	73	Patients were adults with a guideline recommended pacing indication and implanted with Micra.
Hai 2018	Prospective cohort study; China; 2015–2018.	51	81	47	Patients were adults with a class I or IIa indication who received Micra transcatheter pacing system implantation.
Martinez-Sande 2016	Prospective cohort study; Spain; 2015–2016.	30	79	67	Patients were adults ≥65 years of age who had an indication for single chamber ventricular pacing.
Pagan 2020	Retrospective cohort study; United States; 2015–2019.	302 (183 Micra, 119 transvenous)	90	52	Patients were adults ≥85 years of age with Micra transcatheter pacing system implantation and a reference group with transvenous systems.
Reddy 2014	Prospective cohort study; International; 2012–2013.	33	77	67	Patients with a clinical indication for single chamber ventricular pacing.
Reddy 2015	Prospective cohort study; International; 2014–2015.	526	76	62	Patients with a clinical indication for single chamber ventricular pacing.
Reynolds 2016	Prospective cohort study; International; 2015.	725	76	59	Patients with class I or II indication for single chamber ventricular pacing.
Ritter 2015	Prospective cohort study; International; 2013–2014.	140	77	61	Patients with a class I or II indication for single chamber ventricular pacing.
Sperzel 2018	Prospective cohort study; International; 2013–2017.	470	76	63	Patients were adults with indication for single chamber ventricular pacing with life expectancy greater than 1 year.
Tachibana 2020	Retrospective cohort study; Japan; 2014–2019.	62 (27 Micra, 35 transvenous)	90	44	Patients were adults age ≥85 years of age with an indication for single chamber ventricular pacing and a reference group with transvenous system.
Tolosana 2020	Prospective cohort study; Spain; 2014–2018.	110	79	49	Patients were adults with Micra transcatheter pacing system implantation.
Vaidya 2019	Retrospective cohort study; United states; 2014–2017.	180 (90 leadless, 90 TV)	81	63	Patients were adults with Micra and Nanostim transcatheter pacing system implantation, indicated for a single chamber pacemaker.
Valiton 2018	Retrospective cohort study; Switzerland; 2015–2017.	92	80	65	Patients were adults with Micra transcatheter pacing system implantation, indicated for a single chamber pacemaker.
Zucchelli 2020	Prospective cohort study; Italy; 2014–2019.	200 (100 Micra, 100 transvenous)	77	77	Patients with class I indication for single chamber ventricular pacing and a reference group with transvenous systems.

Table 2
Electrical parameters and implant details.

Study ID	Threshold (implant)	R-wave implant	Impedance (Implant)	Threshold at FU	R-wave at FU	Impedance at FU	Procedure duration mean ±SD	Fluoroscopy duration mean ±SD	Redeployments	Implant success
Bongiorni 2018	0.57 ± 0.34 V @ 0.24 ms	10.6 ± 4.9 mV	712 ± 141 Ω	NA	NA	NA	30 ± 16 min	13 ± 7 min	0 = 32 1 = 10 ≥2 = 10	100%
Denman 2018	0.5 V @ 0.24 ms	11.2 mV	754 Ω	NA	NA	NA	Median 29 [IQR 21 to 43] mins	Median 8 min [IQR 5 to 13]	NA	96%
El Amrani 2019	≥90yrs 0.57 V @ 0.24 ms	≥90yrs 10.1 mV	≥90yrs 742 Ω	≥90yrs	≥90yrs	≥90yrs	≥90yrs 26.1 ± 11.6 min	≥90yrs 6.4 ± 4.7 min	<2 =	≥90yrs 97.6%
	<90yrs 0.54 V @ 0.24 ms	<90yrs 10.1 mV	<90yrs 754 Ω	0.56 V @ 0.24 ms	10.8 mV	525 Ω	<90yrs 30.3 ± 14.2 min	<90yrs 7.2 ± 4.9 min	≥90yrs = 39	<90yrs 98.9%
				<90yrs 24 months 0.69 V @ 0.24 ms	<90yrs 14.1 mV	<90yrs 542 Ω			<90yrs = 87	
El-Chami 2018	0.6 V @ 0.24 ms	11.1 mV	730 Ω	0.66 V @ 0.24 ms	13.0 mV	568 Ω	26 min	NA	≤3 = 1523	99.1%
Haeberlin 2020	0.5 V @ 0.24 ms	9.6 mV	690 Ω	0.5 V @ 0.24 ms	12.9 mV	570 Ω	45 [IQR 33-63 IQR] mins	5.9 (3.3–9.0 IQR) mins	0 = 63 1–4 = 29 >4 = 8	95.5%
Hai 2018	0.61 V @ 0.24 ms	9.7 mV	NA	0.61 V @ 0.24 ms	NA	NA	NA	8.2 ± 4.2min	0 = 42 1 = 4 2 = 5	100%
Martinez-Sande 2016	0.59 V @ 0.24 ms	12.3 mV	711 Ω	0.54 V @ 0.24 ms	14.4 mV	566 Ω	NA	NA	NA	100%
Pagan 2020	0.7 ± 0.6 V @ 0.24 ms (Pulse width used in 85.5%)	9.7 ± 4.8 mV	826.8 ± 248.1 Ω	NA	NA	NA	35.7 ± 23 min	4.1 ± 4.8 min	NA	98.4%
Reddy 2014	~0.8 V (ms NA)	~8 mV	~775 Ω	~0.5 mV (ms NA)	~10.5 mV	~600 Ω	28 ± 17 min	NA	0 = 23 1 = 4 2 = 4 3 = 2	97%
Reddy 2015	0.82 V @ 0.4 ms	7.8 mV	700 Ω	0.58 V @ 0.4 ms	9.2 mV	456 Ω	46.5 ± 25.3 min	13.9 ± 9.1 min	0 = 354 1 = 89 2 = 39 >2 = 22	95.8%
Reynolds 2016	0.63 V @ 0.24 ms	11.2 mV	724 Ω	0.54 V @ 0.24 ms	15.3 mV	627 Ω	34.8 ± 24.1 min	8.9 ± 16.6 min	NA	99.2%
Ritter 2015	0.57 V @ 0.24 ms	11.7 mV	719 Ω	0.51 @ 0.24 ms	16.1 mV	651 ohms	37 ± 21 min	9 ± 7 min	0 = 82 1-4 = 52 >5 = 6	100%
Roberts 2017	0.6 V @ 0.24 ms	11.4 mV	721 Ω	0.6 V @ 0.24 ms	NA	572 Ω	NA	NA	≤2 = 615	99.6%
Sperzel 2018	0.8V V @ 0.4 ms	7.2 mV	517 Ω	0.54 V @ 0.4 ms	9.6 mV	738 Ω	36.3 ± 17.2 min	NA	0 or 1 = 435 2 or more: 16	96.6%
Tachibana 2020	1.3 V (ms NA)	7.65 mV	633 Ω	1.19 V (ms NA)	11.5 mV	460 Ω	60.3 ± 22.6 min	NA	NA	100%
Tolosana 2019	~0.5 V @ 0.24 ms	11 mV	~780 Ω	0.5 V @ 0.24 ms	15 mV	~600 Ω	35 ± 11.2 min	NA	0 = 86 1 = 19 2 = 1 3 = 1 4 = 1 5 = 1	98.2%
Vaidya 2019	~ 0.5 V (ms NA)	~10 mV	~675 Ω	~0.5 V (ms NA)	10.5 mV	600 Ω	111 min	8.9 min	NA	100%
Valiton 2018	0.38 V @ 0.24 ms	~12 mV	~600 Ω	~0.5 V @ 0.24 ms	~12.5 mV	~520 Ω	41 ± 22 min	6.7 ± 4.8 min	NA	97.8%
Zucchelli 2020	0.51 V @ 0.24 ms	11.23 mV	692 Ω	~0.5 V @ 0.24 ms	~8.5 mV	~520 Ω	43.9 ± 22 min	12.3 ± 6.8min	0 = 60 1 = 18 2 = 11 >3 = 11	100%

NA = not available; V = volts; ms = milliseconds; mV = millivolts; min = minutes.

outcomes, death and complications associated with implantation and/or follow-up, and electrical parameters at implant and/or follow-up.

Study titles and abstracts returned from the search were screened by independent pairs (DD & JM, NJ & PB, VC & HB) to determine their relevance to this review and exclude those studies that did not meet inclusion criteria. Studies highlighted as potentially relevant were accessed and reviewed (DD & CSK). Relevant data was extracted from the included studies by DD, JM, and BP, and reviewed by CSK. The data extracted from the studies included: study design, sample size, patient characteristics (mean age, gender), inclusion criteria, indications for implant, implant success rate, procedural characteristics, electrical parameters at implant, and complications. Furthermore, we extracted follow-up

Table 3
Follow up and results of included studies.

Study ID	Hospital length of stay	Follow up	Results
Bongiorni 2018	NA	Mean 13 ± 9 months	Death: 2/52 (3.8%) (non-cardiac) Readmissions: 2/52 (3.8%) (acute coronary syndrome and acute heart failure) Infection: 0/52 (0%) Device malfunction: 0/52 (0%) High (≥1 V @ 0.24 ms) at implant: 8/52 (15.4%) Very high (≥1.5 V @ 0.24 ms) at implant: 1/52 (1.9%)
Denman 2018	1 day [IQR 1-2]	Median 355 days (9-905 range)	Unsuccessful implant: 3/79 (3.8%) Acute dislodgment requiring snare retrieval: 1/79 (1.3%) Adverse events within 24hrs: 2/79 (2.5%, VT and pericardial effusion) Death: 5/79 (6.3%) (unrelated to implant) Infection: 0/79 (0%) Device complication: 0/79 (0%)
El Amrani, 2019	3 days (implant indication to discharge)	Mean 342 ± 279 days	Unsuccessful Implant: 2/129 (1.6%) High implant threshold (≥1.5 V @ 0.24 ms): 3/129 (2.3%) Major complications at implant and within 30-days of implant: 3/129 (2.3%) Events at groin puncture site: 2/129 (1.5%) Incision site hematoma: 1/129 (0.8%) Pseudoaneurysm: 1/129 (0.8%) Cardiac perforation: 1/129 (0.8%) Death: 29/129 (22.5%) (all non-device related)
El-Chami, 2018	NA	Mean 6.8 ± 6.9 months	Death (all cause): 144/1817 (7.9%) System or procedure related major complication: Total of major complications: 41/1817 (2.3%) Death (related to procedure): 5/1817 (0.3%) Hospitalisation: 16/1817 (0.9%) Prolonged hospitalisation: 29/1817 (1.6%) System revision: 13/1817 (0.7%) Loss of device function: 9/1817 (0.5%) Within 30-days: Embolism and thrombosis: 2/1817 (0.1%) Events at groin puncture site: 10/1817 (0.6%) Cardiac effusion/perforation: 8/1817 (0.4%) Pacing issues: 12/1817 (0.7%) Infection: 3/1817 (0.2%) Other: 6/1817 (0.3%) >30-days: Embolism and thrombosis: 0/1817 (0%) Events at groin puncture site: 1/1817 (0.06%) Cardiac effusion/perforation: 0/1817 (0%) Pacing issues: 2/1817 (0.1%) Infection: 0/1817 (0%) Other: 2/1817 (0.1%)
Haeberlin 2020	NA	Mean 13 ± 10 months	Death: 25/111 (22.5%) (non-related to procedure or device) Unsuccessful Implant: 5/111 (4.5%) Perioperative complications: 3/111 (2.7%) Tamponade: 1/111 (0.9%) Major bleeding: 1/111 (0.9%) Syncope due to electrical performance: 1/111 (0.9%)
Hai 2018	NA	Median 218.7 days	Death: 6/51 (11.8%) (non-device related) Pericardial effusion: 1/51 (2.0%)
Martinez-Sande 2016	NA	Mean 5.3 ± 3.3 months	Deaths: 0/30 (0%) Displacement: 0/30 (0%) Systemic infection: 0/30 (0%) Pericardial effusion: 1/30 (3.3%) Access related: 0/30 (0%)
Pagan 2020	NA	NA	Unsuccessful Micra Implant: 3/183 (1.6%) Implant complications with Micra vs transvenous pacemaker: Total complications: 6/183 (3.3%) vs 7/119 (5.9%) Hematoma: 5/183 (2.7%) vs 3/119 (2.5%) Pericardial effusion: 1/183 (0.5%) vs 1/119 (0.8%) Lead/device dislodgement: 0/183 (0%) vs 3/119 (2.5%) Procedure related death: 0/183 (0%) vs 0/119 (0%)
Reddy 2014	31 ± 20 h	90 days	Death (procedure related): 1/33 (3.0%) Cardiac tamponade: 1/33 (3.0%) Device positioned in LV requiring removal: 1/33 (3.0%) Vascular injury: 0/33 (0%) Rehospitalization within 90 days: 3/33 (9.1%) Complication free rate: 31/33 (93.9%)
Reddy 2015	1.1 ± 1.7 days	Mean 6.9 ± 4.2 months	Device related serious adverse events:

Table 3 (*continued*)

Study ID	Hospital length of stay	Follow up	Results
			Total: 34/526 (6.5%) Cardiac perforation: 8/526 (1.6%) Vascular complication: 6/526 (1.2%) Arrhythmia during implant: 3/526 (0.6%) Cardiopulmonary arrest during procedure: 1/526 (0.2%) Device dislodgement: 6/526 (1.1) Device migration during implant: 4/526 (0.4%) Elevated threshold requiring reintervention: 4/526 (0.8%) Hemothorax: 1/526 (0.2%) Angina pectoris: 1/526 (0.2%) Pericarditis: 1/526 (0.2%) Acute confusion and expressive aphasia: 1/526 (0.2%) Dysarthria and lethargy after implantation: 1/526 (0.2%) Contrast-induced nephropathy: 1/526 (0.2%) Orthostatic hypotension with weakness: 1/526 (0.2%) Left-leg weakness during implantation: 1/526 (0.2%) Probable pulmonary embolism: 1/526 (0.2%) Ischemic stroke: 1/526 (0.2%)
Reynolds 2016	NA	Mean 4 months	Major complication: 25/725 (3.4%) Death: 1/725 (0.1%) Loss of device functions: 1/725 (0.1%) Hospitalization: 12/725 (1.7%) Prolonged hospitalization: 16/725 (2.2%) System revision: 3/725 (0.4%) DVT: 1/725 (0.1%) Pulmonary thromboembolism: 1/725 (0.1%) Puncture site groin complications: 5/725 (0.7%) Cardiac perforation of effusion: 11/725 (1.6%) Elevated thresholds: 2/725 (0.3%) MI: 1/725 (0.1%) Cardiac failure: 3/725 (0.4%) Metabolic acidosis: 1/725 (0.1%) PPM syndrome: 1/725 (0.1%) Presyncope: 1/725 (0.1%) Syncope: 1/725 (0.1%)
Ritter 2015	2 ± 2 days	1.9 ± 1.8 months	Death (related to procedure): 0/140 (0%) Transient AVB: 4/140 (2.9%) RBBB: 2/140 (1.4%) VT: 2/140 (1.4%) VF: 1/140 (0.7%) Pericardial effusion: 1/140 (0.7%) Acute MI: 1/140 (0.7%) Pericarditis: 1/140 (0.7%) Non-cardiac chest pain: 1/140 (0.7%) Angina pectoris: 2/140 (1.4%) Arterial pseudoaneurysm: 2/140 (1.4%) Incision site hemorrhage: 3/140 (2.1%) Incision site hematoma: 2/140 (1.4%) Incision site pain: 1/140 (0.7%) Incisional drainage: 1/140 (0.7%) Vaso-vagal presyncope: 2/140 (1.4%) Dysuria following procedure: 1/140 (0.7%) Osteoarthritis following procedure: 1/140 (0.7%) Back pain during procedure: 1/140 (0.7%)
Sperzel 2018	1.2 ± 1.7 days	Mean 19.5 ± 11.5 months Serious adverse device effects reported at 180 days	In 300 subject primary cohort: Freedom from adverse events at 6 months was 94.6% in 89% of cohort. Total cohort: Cardiac perforation: 2/470 (0.4%) Cardiac tamponade: 7/470 (1.5%) Pericardial effusion: 2/470 (0.4%) Device dislodgement: 2/470 (0.4%) Vascular complications: 1/470 (1.1%) Cardiac arrhythmia/AVB: 4/470 (0.9%) Failure to/loss of capture: 2/470 (0.4%) Battery failure: 19/470 (4%) Hematoma: 1/470 (0.2%) PPM syndrome: 1/470 (0.2%) Progression of HF: 1/470 (0.2%) Syncope: 1/470 (0.2%) Thromboses 1/470 (0.2%) Death: 1/470 (0.2%)
		6 Months	Leadless vs transvenous pacemaker:

(*continued on next page*)

Table 3 (*continued*)

Study ID	Hospital length of stay	Follow up	Results
Tachibana 2020	Leadless: 9.7 ± 6.8days Transvenous: 11.2 ± 5.8 days		Death: 4/27 (14.8%) vs 4/35 (11.4%) Haematoma: 0/27 (0%) vs 2/35 (5.7%) Pocket infection: 0/27 (0%) vs 2/35 (5.7%) Infective endocarditis: 1/27 (3.7%) vs 1/35 (2.9%) Device dislodgement: 1/27 (3.7%) vs 1/35 (2.9%) DVT: 1/27 (3.7%) vs 0/35 (0%) Complication free rate: 25/27 (92.6%) vs 31/35 (88.6%), p = 0.68
Tolosana 2020	NA	Mean 24 ± 16 months	Death: 18/110 (16.4%) Procedure related complications: 3/110 (2.7%) Pericardial effusion: 1/110 (0.9%) DVT: 1/110 (0.9%) Loss of capture: 1/110 (0.9%) High implant threshold (>1 V @ 0.24 ms): 12/110 (10.9%) High FU threshold (increased to >2 V @ 0.24 ms): 4/110 (3.6%)
Vaidya 2019	NA	Mean 62 days	Devices implanted: Micra 73, Nanostim 17 and transvenous 90. Leadless vs transvenous complications: Death (non-implant related): 1/90 (1.1%) vs 1/90 (1.1%) Procedure related major complications: 0/90 (0%) vs 1/90 (1.1%), p = 0.24 Procedure related minor complications: 7/90 (7.8%) vs 3/90 (3.3%), p = 0.19 Pericardial effusion: 2/90 (2.2%) vs 3/90 (3.3%), p = 0.50 Any infection: 2/90 (2.2%) vs 3/90 (3.3%), p = 0.69 Device endocarditis: 0/90 (0%) vs 3/90 (3.3%), p = 0.04 Device malfunction: 1/90 (1.1%) vs 1/90 (1.1%), p = 0.24 Device related revision/extraction: 3/90 (3.3%) vs 4/90 (4.4%), p = 0.70
Valiton 2018	NA	Mean 12.4 ± 7.4 months	Death (non-device or implant related): 19/92 (20.6%) Death (implant related): 1/92 (1.1%) Major perioperative complications: 6/92 (6.5%) Cardiac perforation and tamponade: 2/92 (2.2%) Haematoma: 1/92 (1.1%) Thrombus: 1/92 (1.1%) VT: 1/92 (1.1%) Musculoskeletal pain: 1/92 (1.1%) Major complications during follow up: 3/92 (3.3%) High threshold requiring revision: 2/92 (2.2%) VT requiring revision: 1/92 (1.1%) High threshold 1 day post implant (≥2 V @ 0.24 ms): 4/92 (4.3%) High threshold 1,6 and 12 month post implant (≥2 V @ 0.24 ms): 6/92 (6.5%)
Zucchelli 2020	NA	Median 12 months	Leadless vs transvenous complications: Acute complications: 0/100 (0%) vs 7/100 (7%), p = 0.02 Pneumothorax: 0/100 (0%) vs 1/100 (1%), p = 1.00 Pericardial effusion: 0/100 (0%) vs 1/100 (1%), p = 1.00 Pocket hematoma: 0/100 (0%) vs 2/100 (2%), p = 0.47 Lead dislodgment: 0/100 (0%) vs 3/100 (3%), p = 0.24 Long-term complications: 0/100 (0%) vs 3/100 (3%), p = 0.24 Device endocarditis: 0/100 (0%) vs 1/100 (1%), p = 1.00 Worsening of LVEF: 0/100 (0%) vs 2/100 (2%), p = 0.47 Overall complications: 0/100 (0%) vs 10/100 (10%), p = 0.004 Overall device revisions: 0/100 (0%) vs 6/100 (6%), p = 0.038 Total deaths: 7/100 (7%) vs 23/100 (23%), p = 0.003 Non-cardiac deaths: 7/100 (7%) vs 15/100 (15%), p = 0.11 Not device-related cardiac deaths: 0/100 (0%) vs 7/100 (7%), p = 0.02 Device-related deaths: 0/100 (0%) vs 1/100 (1%), p = 1.00

NA=Not applicable; IQR=Interquartile range; VT=Ventricular tachycardia; DVT = Deep vein thrombosis; MI = Myocardial infarction; PPM=Permanent pacemaker; AVB = Atrioventricular block; RBBB = Right bundle branch block; VF=Ventricular fibrillation; HF=Heart failure; FU=Follow-up; LVEF = Left ventricular ejection fraction.

data regarding complications and electrical parameters at last follow-up. The study quality assessment was considered by using the Newcastle-Ottawa scale [11].

2.4. Data analysis

Collected data was presented in tables and described in the text by considering averages across mean values or range reported by the individual studies. Statistical synthesis was performed using two methods depending on the availability of a transvenous comparison group. RevMan 5.4 (Nordic Cochrane Centre, Kobenhavn, Demark) was used to conduct random-effects meta-analysis using the Mantel-Haenszel method for pooled risk rations from dichotomous data for studies which reported both outcomes for patients with leadless pacemakers and transvenous pacemakers. Statistical heterogeneity was evaluated using the I^2 statistic and I^2 values of 30–60% represents a moderate level of heterogeneity [12]. The statistical heterogeneity was explored with leave-one-out analysis for pooled analyses where there were more than two studies and statistical heterogeneity greater than moderate heterogeneity (I^2>60%). For studies which only included patients with leadless pacemakers, Microsoft Excel was used to pool the results from

individual studies which reported similar adverse outcomes as described previously [13]. Additional analysis was performed by excluding cohort which had age restrictions.

3. Results

3.1. Study selection and description

After review of the titles and abstracts from the studies retrieved from the search, a total of 18 studies were included [9,14–30]. (Supplementary Fig. 1).

18 studies that met the inclusion criteria were included. These studies consisted of 14 prospective cohort studies and 4 retrospective cohort studies and 6 were international multicentre cohorts (Table 1). These studies took place between 2012 and 2019. The 18 studies evaluated 2496 patients with leadless pacemaker implants and 4 studies which included a transvenous pacemaker reference group with a total of 344 patients. The average age of participants in the included studies was 80 years and the proportion of male patients was 62%. The exclusion criteria and indication for leadless pacemaker insertion of the included studies are presented in Supplementary Tables 2 and 3, respectively.

The capture threshold, R-wave amplitude and impedance at implant and follow-up as well as the procedural duration and fluoroscopy duration is shown in Table 2. A total of 8 studies reported the number of redeployments and 31.9% (347/1089) cases had to have one or more redeployment. Implant success rate ranged from 95.5% to 100% across the 18 studies.

3.2. Quality assessment

Quality assessment of the studies is shown in Supplementary Table 4. There were 14 prospective cohort studies and 4 retrospective cohort studies. All studies had reliable ascertainment of leadless pacemaker insertion and all but one study had a clear explanation of reliable methods for ascertaining outcomes. Data that was missing or lost to follow-up was significant in 3 studies. Most studies were generalizable to a cohort of adults who had an indication for pacing but three studies had additional age restrictions.

3.3. Pooled analysis of events across studies of leadless pacemakers

The results and follow up of patients with leadless pacemakers are presented in Table 3 and the pooled rate of adverse outcomes with leadless pacemakers is shown in Fig. 1. While all-cause mortality was occurred in 6.11% of patients, only 0.29% of patients had procedure or device related deaths (Supplementary Table 5). The causes of death are shown in Supplementary Table 6. Any complication, high threshold or unsuccessful implant each occurred in approximately 3% of patients. Pericardial effusions and cardiac tamponade occurred in 0.96% and 1.47% of patients, respectively. Other complications such as device dislodgement, device revision, device malfunction, access site complications and infection occurred in less than 1% of patients. Additional analysis excluding patients from cohorts with age restrictions yielded similar results (Supplementary Table 7).

3.4. Meta-analysis of studies of leadless vs transvenous pacemakers

A total of 4 studies included both a leadless pacemaker group as well as a transvenous group, with a total of 400 patients in the leadless pacemaker group and 344 patients with transvenous systems. Meta-analysis of these studies suggests that there was no difference in hematoma (RR 0.67 95%CI 0.21–2.18, 3 studies), pericardial effusion (RR 0.59 95%CI 0.15–2.25, 3 studies), device dislocation (RR 0.33 95%CI 0.06–1.74, 3 studies), any complication (RR 0.44 95%CI 0.17–1.09, 4 studies) and death (RR 0.45 95%CI 0.15–1.35, 2 studies) between the two groups (Fig. 2).

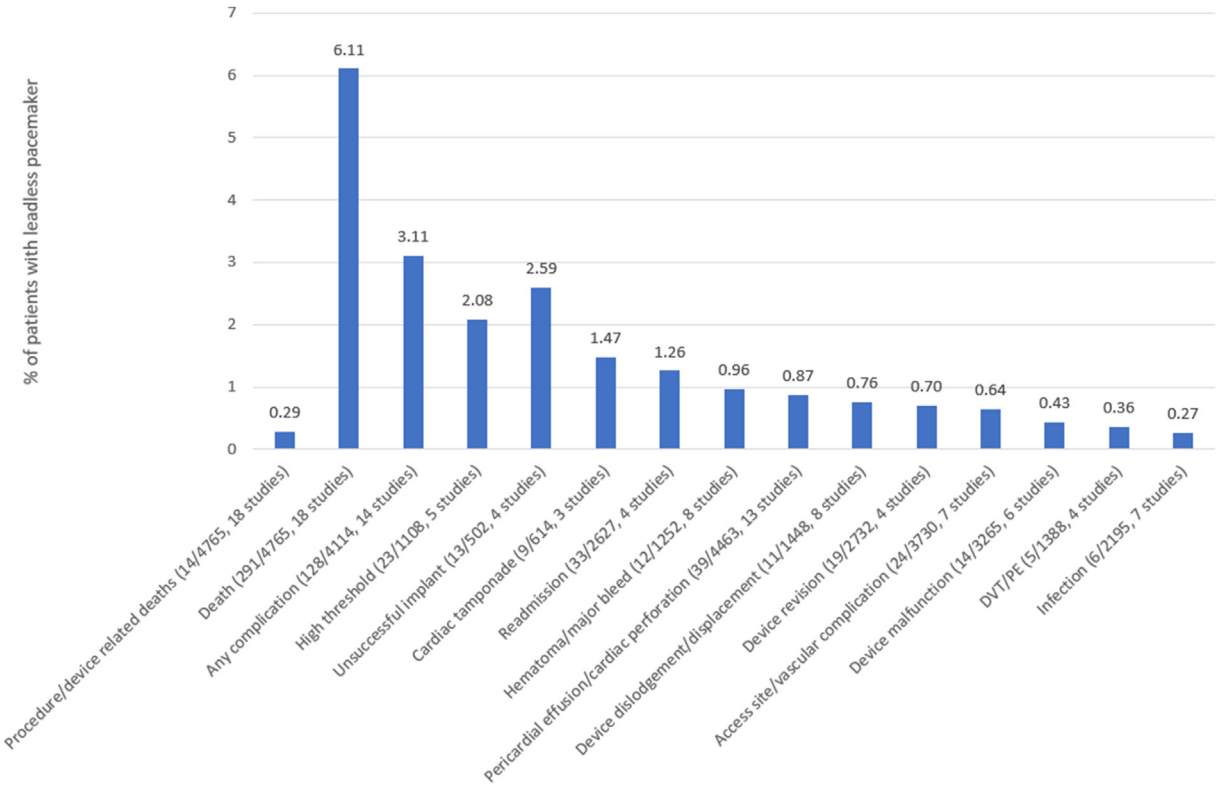

Fig. 1. Results of pooled analysis of studies of leadless pacemakers.

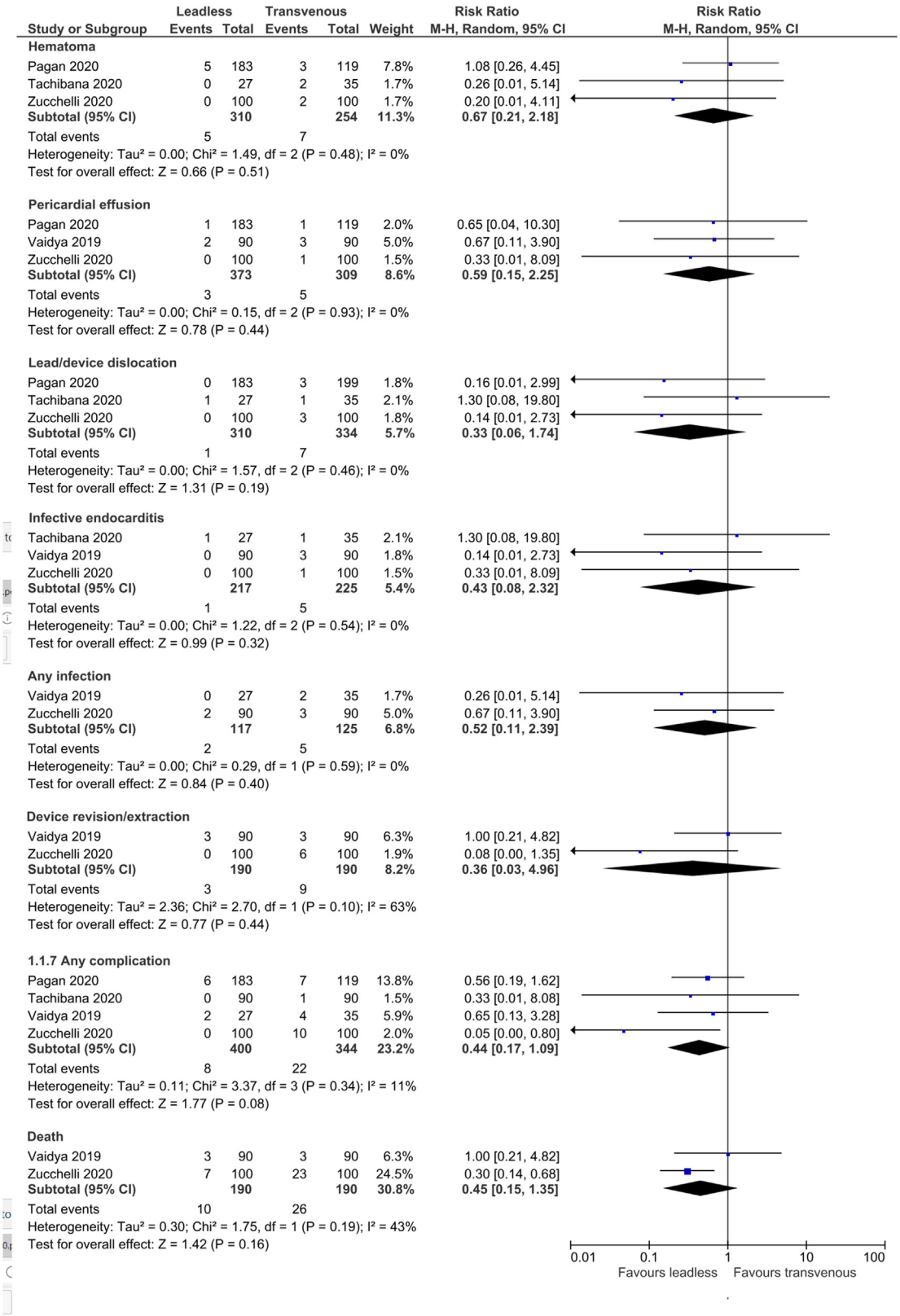

Fig. 2. Results of meta-analysis of studies comparing leadless to transvenous systems.

4. Discussion

This systematic review of 18 studies reports the safety and efficacy of leadless pacemakers. Pooled analysis of the literature showed implant success rates ranging between 95.5 and 100% with low rates of peri- and post-procedural complications particularly procedure or device related death. Furthermore, meta-analysis of those studies which included both transvenous and leadless

pacemakers reported no statistical difference in outcomes, with a trend towards fewer complications in the leadless pacemaker cohort. These findings suggest that leadless systems are a safe and viable alternative to transvenous systems, but more understanding is needed to help determine patient selection for leadless systems.

The largest of the studies to be included in this analysis was conducted by El-Chami et al. (2018), who reported the real-world outcomes of 1817 patients implanted with the Micra pacing system and reported an implant success rate of 99.1% [16]. The lowest implant success rate (95.5%) seen in this analysis of the literature came from two experienced electrophysiology centres in Switzerland who had limited experience with leadless pacemaker implantation [17]. Unsuccessful implants were reportedly mainly due to challenging venous or cardiac anatomy which made catheter-guided delivery of the devices difficult.

The most common adverse event in this study was death (6.1%), the majority of these being related to non-cardiac causes. The mean age of participants across all included studies was 80 years and many of these had multiple cardiac and non-cardiac co-morbidities. However, if one considers death related to the procedure or device, the rate is much lower (0.3%). In this analysis, we report a pooled complication rate of 3.11%. This appears to be lower than the 6.8% rate of any complication reported by a Danish nationwide cohort of patients receiving a single chamber pacemaker [2]. The most common complication in our analysis was a high capture threshold (at implant or follow-up) which was seen in 2.87% of cases. However, differences in definition of high threshold between studies make it difficult to assess the significance of this finding. Furthermore, we do not know how many of these patients required re-intervention due to high threshold or were managed with programming alterations only. As is the case with transvenous pacemakers, increases in threshold can have an impact on battery longevity but this may be minimal if patients have a low burden of ventricular pacing.

It is well established that lead related complications in transvenous devices can occur both during the short and long-term stages of pacemaker follow-up. Total lead related complications reportedly occur in 2.8% of new cases, with lead related reintervention occurring in approximately 2.4% of cases [2]. Lead-related complications are completely avoided with the leadless pacemaker and this significantly reduces the procedural and infection risk associated with reintervention. Our study does however show a 0.76% incidence of leadless pacemaker dislodgement/displacement. It is important to note that most device dislodgements occurred in patients implanted with the Nanostim leadless pacemaker which utilised an active fixation mechanism and is now no longer commercially available.

The avoidance of both short and long-term lead related complications may be of increased clinical significance in younger patients who would be likely to require pacing therapy in the long-term, thus increasing the duration that an implant is required and increasing the risk of potential complications due to the presence of the device for a longer time-frame. It is well reported that the risk of transvenous lead complication, in addition to the risk of lead extraction, increases with the age of the lead and this is a major consideration for younger patients who require bradycardia pacing [31]. Leadless pacemaker implantation may be a viable option to reduce the risks associated with transvenous leads in this population. However, there has been limited research into the use of these devices in a younger cohort. There are also several other considerations which should be investigated such as the real-world longevity and battery-life of the device and the implication of multiple leadless devices co-existing in the right ventricle and their potential effect on cardiac function and structure.

To the best of our knowledge, this is the first systematic review of leadless pacemakers. However, this study was limited by small sample sizes of included studies, with several included studies reporting the outcomes of less than 100 patients and significant heterogeneity between studies. However, leadless implantable cardiac pacemakers are relatively recent in widespread usage and the analysis included both experienced and inexperienced centres which would balance variability due to implanter learning curve and increase to the generalizability of the findings. Only four of the studies in this review included a transvenous pacemaker control group and all of these were non-randomised studies which may have resulted in a degree of selection bias. Finally, in this analysis most of the studies were pooled with weighting based on the sample size because many of the included studies were single arm and lacked a control group. This approach has limitations as studies can have very different populations resulting in variable event rates which may introduce biases in the results.

In conclusion, this systematic review affirms high levels of safety and efficacy of leadless pacemakers in patients who have an indication for single chamber ventricular pacing, at levels that appear to be comparable to transvenous pacemakers. However, due to the fact that leadless pacemaker technology and widespread usage is relatively recent, randomized trials are lacking, evidentiary value of the current review is diminished.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ipej.2021.12.001.

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