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Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis

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Infectious complications after cardiac implantable electronic device (CIED) implantation are increasing over time and are associated with substantial mortality and healthcare costs. The aim of this study was to systematically summarize the literature on risk factors for infection after pacemaker, implantable cardioverter-defibrillator, and cardiac resynchronization therapy device implantation. Electronic searches (up to January 2014) were performed in PubMed, Scopus, and Web of Science databases. Sixty studies (21 prospective, 9 case–control, and 30 retrospective cohort studies) met the inclusion criteria. The average device infection rate was 1–1.3%. In the meta-analysis, significant host-related risk factors for infection included diabetes mellitus (odds ratio (OR) [95% confidence interval] = 2.08 [1.62–2.67]), end-stage renal disease (OR = 8.73 [3.42–22.31]), chronic obstructive pulmonary disease (OR = 2.95 [1.78–4.90]), corticosteroid use (OR = 3.44 [1.62–7.32]), history of the previous device infection (OR = 7.84 [1.94–31.60]), renal insufficiency (OR = 3.02 [1.38–6.64]), malignancy (OR = 2.23 [1.26–3.95]), heart failure (OR = 1.65 [1.14–2.39]), pre-procedural fever (OR = 4.27 [1.13–16.12]), anticoagulant drug use (OR = 1.59 [1.01–2.48]), and skin disorders (OR = 2.46 [1.04–5.80]). Regarding procedure-related factors, post-operative haematoma (OR = 8.46 [4.01–17.86]), reintervention for lead dislodgement (OR = 6.37 [2.93–13.82]), device replacement/revision (OR = 1.98 [1.46–2.70]), lack of antibiotic prophylaxis (OR = 0.32 [0.18–0.55]), temporary pacing (OR = 2.31 [1.36–3.92]), inexperienced operator (OR = 2.85 [1.23–6.58]), and procedure duration (weighted mean difference = 9.89 [0.52–19.25]) were all predictors of CIED infection. Among device-related characteristics, abdominal pocket (OR = 4.01 [2.48–6.49]), epicardial leads (OR = 8.09 [3.46–18.92]), positioning of two or more leads (OR = 2.02 [1.11–3.69]), and dual-chamber systems (OR = 1.45 [1.02–2.05]) predisposed to device infection. This systematic review on risk factors for CIED infection may contribute to developing better infection control strategies for high-risk patients and can also help risk assessment in the management of device revisions.

Keywords Infection • Pacemaker • Defibrillator • Resynchronization • Risk factors • Predictors

Introduction

Cardiac implantable electronic devices (CIEDs), including permanent pacemakers (PPMs) and implantable cardioverter-defibrillators (ICDs), are increasingly being used in cardiac disease management.[1] An analysis of the Nationwide Inpatient Sample discharge records from 1993 through 2008 showed a 96% increase in CIED implantations in the USA. During the same period, the incidence of CIED infection increased by 210% (from 1.5% in 1993 to 2.4% in 2008).[2] Infection is a serious complication of cardiac device implantation and is associated with substantial morbidity, mortality, and healthcare costs. In-hospital mortality rates have been reported to be 3.7–11.3%.[2–7] The standard-of-care requires device removal and systemic antibiotic therapy.[8] The additional admission costs of an infected device can exceed $15 000 in the USA and €7000 in Europe.[5,9]

A previous meta-analysis of randomized controlled trials concluded that antibiotic prophylaxis reduces the risk for device-related infectious complications.[10] There is also evidence that CIED infection may be related to patient comorbidities,[11,12] device type,[13,14] and the number of device-related interventions.[15,16] Several studies have attempted to identify risk factors associated with CIED infection. However, most of these investigations are limited by their retrospective study design; examination of a single or a few variables; and conflicting rather than conclusive results. It is also possible that

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the sample size of individual studies is relatively small to reveal significant results. The latest update on CIED infections by the American Heart Association discussed the need for larger studies assessing risk factors for device-related infections.[17] In this context, we performed the first, to our knowledge, systematic review and meta-analysis of the available evidence on potential host-, procedure-, and device-related risk factors for infection after CIED implantation.

Methods

Data sources

Two reviewers (K.A.P. and A.A.K.) independently conducted a systematic literature search on PubMed, Web of Science, and Scopus databases up to January 2014. The following search terms were applied: (pacemaker* OR defibrillator* OR resync*) AND (infect* OR endocarditis) AND (risk OR predict*). The references of relevant articles were also hand-searched. No restrictions in the language or year of publication were imposed. Unpublished studies reported as conference abstracts were included in the systematic review if they provided relevant data.

Study selection

To be considered for inclusion in the systematic review, a study should meet the following inclusion criteria: examine potential risk factors for CIED infection that have been examined by at least two studies; include patients undergoing *de novo* implantation or replacement/revision/upgrade of a PPM, ICD, or cardiac resynchronization therapy (CRT) device. Both prospective and retrospective studies were considered eligible. Overlapping studies were included in the systematic review only if they had examined different risk factors. Finally, we excluded studies on paediatric populations,[18] and studies examining risk factors for cardiac device infection in patients with bloodstream infection.[19]

Data extraction

Two reviewers (K.A.P. and A.A.K.) independently extracted the following data: design and year of study, definition of CIED infection, population characteristics, follow-up, infection rate, causative pathogens, potential host-, procedure-, and device-related risk factors. Any disagreement was resolved by consensus in meetings that involved all authors. When study data were not fully available, additional information was requested from the corresponding authors.

Definition

The CIED definitions used in the included studies are reported in Supplementary material online, *Table S1*. According to the Mayo Cardiovascular Infections Study Group and others, clinical evidence of CIED infection is defined as the presence of local signs of inflammation at the generator pocket including erythema, warmth, tenderness, fluctuance, wound dehiscence, erosion, or purulent drainage. Cardiac implantable electronic device-related endocarditis is clinically confirmed by the presence of valvular or lead vegetations in echocardiography, or when the Duke criteria for infective endocarditis are met.[20] Infection is microbiologically confirmed by positive cultures from the device pocket, electrode leads, or blood. The definition also includes cases of positive blood cultures without local inflammatory signs, no other source of bacteraemia, and resolution of bacteraemia after device extraction.[6,21,22] There are no gold standard criteria for the diagnosis of device infection, and therefore no exclusions were made on the basis of CIED infection definition. However, sensitivity analysis was performed excluding studies whose definition was deemed inadequate.

Data analysis and statistical methods

After data extraction, a descriptive data synthesis was performed by summarizing significant risk factors for CIED infection identified in univariate and multivariate analyses of individual studies. Quantitative meta-analyses for factors examined in at least two studies were conducted using Comprehensive Meta Analysis Version 2.[23] Unadjusted infection data were pooled to calculate odds ratio (OR), weighted mean difference (WMD), and 95% confidence intervals (95% CIs) by the use of the DerSimonian–Laird random-effects model.[24] Heterogeneity was assessed by using the Cochrane's Q-statistic and the I^2-statistic, and was considered significant if $P < 0.1$ (Q-statistic) or $I^2 \geq 30\%$ (I^2-statistic).[25] For risk factors examined in at least five studies, publication bias was assessed by inspection of funnel plot asymmetry and by the use of Egger's test of the intercept.[26] Egger's test is the statistical analogue of the visual inspection of funnel plot asymmetry. It is limited, however, by its low power in meta-analyses including a small number of studies. Publication bias was considered significant, if the P value for the test was <0.1. Furthermore, we conducted sensitivity analysis by the use of Duval and Tweedie's trim and fill method, which estimates the number of hypothetical negative unpublished studies and adjusts for publication bias by estimating the effect that missing studies would have had on the outcome of the meta-analysis. Limitations of this method include the assumption of funnel plot symmetry and the fact that it considers publication bias as the only cause of asymmetry.[27] Finally, pre-specified sensitivity analyses were performed by excluding studies with inadequate definition of device-related infection or retrospective studies.

Results

Descriptive data synthesis

The database search yielded a total of 2317 potentially relevant articles, of which 60 met our inclusion criteria and were included in the systematic review (*Figure 1*). Twenty-one studies had prospective design (8 randomized trials,[28–35] 13 prospective cohorts[36–48]) (*Table 1*), whereas 39 were retrospective studies (9 case–control studies,[11,15,16,49–54] 30 retrospective cohorts[12–14,55–81]) (*Table 2*). Staphylococcal species accounted for more than half of the infections (*Staphylococcus aureus*: 30%; coagulase-negative *Staphylococcus*: 25%), while multiple micro-organisms (6%) and Gram-negative bacteria (5%) caused a minority of infections (see Supplementary material online, *Figure S1*). The microbiology of CIED infections is described in Supplementary material online, *Table S2*.

Prospective studies

Twenty-one prospective studies, including a total of 26 172 patients (mean age 70.9 years; 66.9% male), examined at least one potential risk factor for the development of CIED infection. Sixteen studies reported on PPM-related,[28–40,45,46,48] 7 on ICD-related,[30,40,41,42,44,45,48] and 8 on CRT-related infections.[30,40,41,43–45,47,48] The average device infection rate was 1.6% (or 1.2% after excluding superficial wound infections). In multivariate analysis, lack of antibiotic prophylaxis,[30,40] device replacement,[40,43] and reintervention[40,47] were significant risk factors for infection in two studies each, while dialysis,[47] chronic obstructive pulmonary disease (COPD),[43] temporary pacing,[40] fever,[40] ICD device,[47] procedure duration,[47] and haematoma[30] in one study each. Detailed information on significant risk factors in univariate or multivariate analyses of the included studies is presented in *Table 3*.

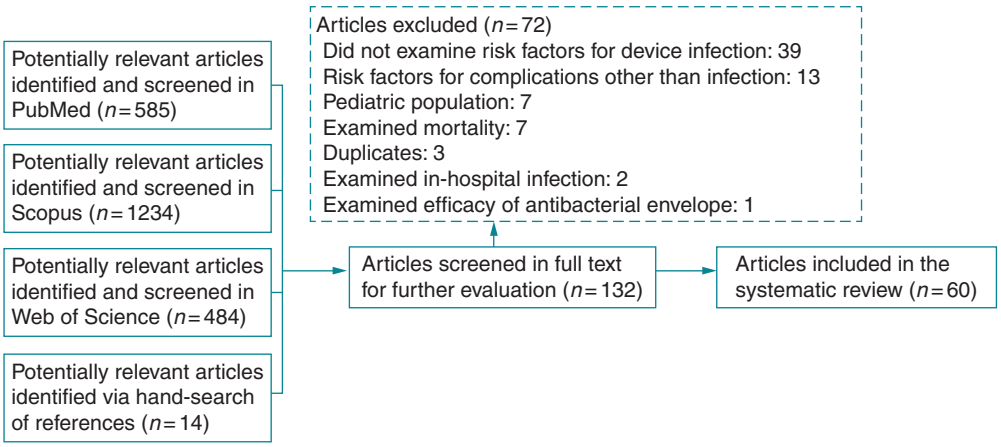

Figure 1 Flow diagram of the selection process of the included studies.

Table 1 Characteristics of the included studies (prospective studies)

Study ID	Totals (*n*)	Male (%)	Age (yrs)[a]	Follow-up (mo)[b]	Infection rate (%)[c]	Identified risk factors[d]
Muers 1981[34]	431	NR	70	22.8 (9–40)	2.1	Lack of antibiotic prophylaxis
Ramsdale 1984[35]	500	50	72	3–12	4.2 (0.6)	–
Bluhm 1984[28]	100	51	73	1–43	8	Lack of antibiotic prophylaxis
Bluhm 1986[29]	106	54	75	14 (7–35)	0	–
Glieca 1987[31]	200	66	66	NR	6	Lack of antibiotic prophylaxis
Mueller 1990[46]	333	57	73	16	0.9	–
Bru 1991[38]	209	53	70	(1–36)	1.4	–
Lüninghake 1993[32]	302	NR	NR	(12–48)	5	–
Mounsey 1994[33]	656	55	74	19 (9–26)	2	Lack of antibiotic prophylaxis; reintervention; procedure duration; inexperienced operator
Chauhan 1994[39]	2019	56	NR	1.5	0.8	Temporary pacing
Aggarwal 1995[36]	1059	51	75	2	1.8 (0.9)	Temporary pacing wire
Kron 2003[42]	539	79	65	27	2.6 (2)	Lack of antibiotic prophylaxis; abdominal pocket
Bertaglia 2006[37]	852	56	77	25.6	1.8 (0.7)	Generator replacement; male sex; shorter procedure duration
Klug 2007[e,40]	6134	60	73	12	0.7	Lack of antibiotic prophylaxis*; temporary pacing*; re-intervention*; fever within 24 h before implantation*; device replacement*
Oliveira 2009[30]	649	47	64	6	2 (1.4)	Lack of antibiotic prophylaxis*; procedure duration; haematoma*; generator replacement
Romeyer-Bouchard 2010[47]	303	81.5	70	31	4.3	Reintervention*; procedure duration*; haemodialysis*; haematoma; ICD device type*; lead dislodgement
Krahn 2011[41]	1081	82	66	1.5	2.6 (1.7)	Haematoma
Metais 2011[45]	304	69	70	12	2.3	Reintervention; anticoagulant/antiplatelet drug use; history of contralateral implant
Landolina 2011[43]	3253	80	67	Median: 18	1/100 pt-yrs	Generator replacement*; COPD*
MacFadden 2012[44]	5213	79	65	12	1.9 (1)	–
Uslan 2012[48]	1744	68	70	6	1.3 (0.8)	Abdominal pocket; haematoma

NR, not reported; yrs, years; mo, months; pt, patient; ICD, implantable cardioverter-defibrillator; COPD, chronic obstructive pulmonary disease.
[a]Mean values are reported unless otherwise stated.
[b]Mean values (range) are reported unless otherwise stated.
[c]The rate of infection after exclusion of minor/superficial infections is reported in parentheses.
[d]Factors marked with asterisk (*) were identified as independent predictors of infection in multivariate analysis.
[e]Male (%) and age refer to 6319 subjects, while infection rate refers to 6134 subjects with available relevant data.

Table 2 Characteristics of the included studies (retrospective studies)

Study ID	Totals (*n*)	Male (%)	Age (yrs)[a]	Follow-up (mo)[b]	Infection rate (%)[c]	Identified risk factors[d]
Case–control studies						
Bloom 2006[11]	4856	77	67	NR	1.6	Generator replacement*; diabetes mellitus; renal insufficiency*; oral anticoagulants*; CHF*; male sex*; age
Sohail 2007[16]	12 799	76	63	39	0.23	Lack of antibiotic prophylaxis*; device replacement/upgrade; CVC; malignancy; corticosteroids*; history of device infection; number of device-related procedures (>2); number of leads (>2)*
Marschall 2007[52]	116	63	62	NR	16.4	Device replacement/revision; abdominal pocket
Lekkerkerker 2008[51]	3410	73	60.5	NR	2.2	Device replacement/revision*; diabetes mellitus; renal insufficiency*; elevated serum Cr; oral anticoagulants*
Gould 2008[49]	451	72	67	12	4 (2.2)	Consultant operator
Nery 2010[53]	2417	67	68.5	NR	1 (0.9)	Generator replacement*; lead dislodgement; dual/triple-chamber device*
Sohail 2011[15]	204	81	Median: 65.5	44.4	NA	Temporary pacing; haematoma; haemodialysis; COPD*; history of device infection; chronic skin disorders; number of device-related procedures (≥3); duration of hospital-stay (≥2 d)*; Charlson index (≥4); epicardial lead*; any post-operative complication*
Raad 2012[54]	72	72	70	NR	NA	Generator/lead replacement; haematoma; dual-chamber device; history of device infection; post-procedural trauma
Herce 2013[50]	2868	60	73	NR	1.2	Reintervention; diabetes mellitus*; dual-chamber device*; heart disease*; simultaneous invasive procedure
Retrospective cohorts						
Rao 1974[72]	401	55.4	NR	NR	0.75	–
Mugica 1977[70]	2016	NR	NR		2	Lack of antibiotic prophylaxis
Hartstein 1978[65]	298	59.8	72	NR	3	Use of drains
Wunderly 1990[77]	263	NR	NR	19	3	–
Trappe 1995[76]	335	91	56	22	3.9	Epicardial lead placement
Spinler 1998[12]	171	80	61	(15.6–102)	4.5	Diabetes mellitus*
Smith 1998[74]	1831	78	63	NR	1.2	Presence of subcutaneous defibrillation patch*
Harcombe 1998[64]	2621	59	74	NR	0.7	Device replacement
Kiviniemi 1999[68]	446	41	72	27 (0–72)	1.8	–
Higgins 2000[66]	174	84.5	69	NR	1.7	Device upgrade to dual chamber
Mela 2001[69]	1406	NR	NR	35	1.2	Abdominal pocket
Wiegand 2004[13]	3164	58	72	3	0.3	ICD device type
Al-Khatib 2005[55]	9854	78	>65	3	1.1	Operator experience*
Gil 2006[63]	423	86	60	NR	2.4	Abdominal pocket; two-stage surgery; subcostal approach of lead placement; trauma at pocket; decubitus ulcer
Catanchin 2007[59]	1481	56	Median: 75	Median: 29.3	1.6	Male sex; number of prior procedures (>1)
Dasgupta 2007[62]	164	71	65	NR	3 (1.8)	–
Ito 2009[78]	71	80	58	37.6	1.4	–
Pakarinen 2010[71]	567	51	72	3	1.9 (1.2)	Reintervention; temporary pacing
Cengiz 2010[60]	890	57	Range: 18–104	34.8	2.5	Lack of antibiotic prophylaxis*; generator replacement*; haematoma; anticoagulants; corticosteroids; CVC*; age*
Borleffs 2010[58]	3161	80	62	38	1.2/100 ICD-yrs	Device (generator/lead) replacement
Margey 2010[e,14]	3105	69	Median: 69	NR	1.3	CRT device*; number of leads (>2); screening time

Continued

Table 2 *Continued*

Study ID	Totals (*n*)	Male (%)	Age (yrs)[a]	Follow-up (mo)[b]	Infection rate (%)[c]	Identified risk factors[d]
Bloom 2011[57]	624	68	70	1.9	0.5	–
Johansen 2011[f,67]	56 657	54	Median: 76	NR	7.14/1000 PPM-yrs	Lack of antibiotic prophylaxis*; device replacement; dual-chamber device; male sex*; younger age (20–49 yrs)*; implantation during the early yrs of study*; procedure complexity; number of prior procedures*; indication (AV block)
Charytan 2011[61]	9528	70	64.5	16.8	4.2/100 pt-yrs	COPD; age; black race (vs. caucasian); dialysis modality (vs. haemodialysis)*; recent infection*; cerebrovascular accident/ TIA*; GI bleeding
Tompkins 2011[75]	1440	65	65	2	0.5	Renal insufficiency; end-stage renal disease
Lyman 2011[81]	38 992	77	66	3	1.2	–
Armaganijan 2012[56]	4814	57	76	61.2	NR	–
Schuchert 2013[73]	402	79	68	12	1.2	–
Peterson 2013[80]	32 034	74	74	3	0.7	–
Palmisano 2013[79]	2671	57	74	Median: 27	1.1	Generator replacement/system upgrade*; CRT device*

NR, not reported; NA, not applicable; yrs, years; mo, months; d, days; pt, patient; PPM, permanent pacemaker; ICD, implantable cardioverter-defibrillator; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CVC, central venous catheter; Cr, creatinine; CRT, cardiac resynchronization therapy; AV, atrioventricular; TIA, transient ischaemic attack; GI, gastrointestinal bleeding.
[a]Mean values are reported unless otherwise stated.
[b]Mean values (range) are reported unless otherwise stated.
[c]The rate of infection after exclusion of minor/superficial infections is reported in parentheses.
[d]Factors marked with asterisk (*) were identified as independent predictors of infection in multivariate analysis.
[e]Male (%) and age refer only to cases.
[f]Male (%) and age refer to patients undergoing first implantation during the study period.

Case–control studies

Nine case–control studies, including 352 cases (mean age 64.5 years; 77% males) and 614 controls (mean age 66.4 years; 72.8% males), examined potential factors predisposing to CIED infection.[11,15,16,49–54] Seven studies reported on PPM-related,[11,16,50–54] 7 on ICD-related,[11,15,49,51–54] and 2 on CRT-related infections.[51,53] The average reported infection rate was 1%. In multivariate analysis, device replacement was independently associated with CIED infection in three studies,[11,51,53] renal insufficiency and anticoagulation therapy in two studies each,[11,51] whereas lack of antibiotic prophylaxis,[16] male gender,[11] congestive heart failure,[11] diabetes mellitus,[50] COPD,[15] corticosteroid use,[16] dual-chamber system,[50] >2 leads,[16] and the presence of epicardial leads[15] in one study each.

Retrospective cohort studies

Thirty retrospective cohort studies, including 180 004 patients/procedures (mean age 69.4 years; 67.4% males), examined at least one potential predictor of cardiac device-related infection.[12–14,55–81] Of these, 16 studies reported on PPM-related,[13,14,56,57,59,60,62,64,65,67,68,70–72,75,79] 22 on ICD-related,[12–14,55,57–63,66,69,71,74–81] and 11 on CRT-related infections.[14,57–59,61,62,67,71,73,75,79] The average rate of infection was 1.2%. In multivariate analysis, age independently predicted CIED infection in three studies,[14,60,67] while device replacement,[60,79] lack of antibiotic prophylaxis,[60,67] and CRT[14,79] in two studies each. Other independent predictors of infection included male gender,[67] diabetes,[12] the presence of a central venous catheter (CVC),[60] greater number of prior device procedures[67] and operator inexperience.[55]

Meta-analysis

Pooled estimates for potential factors predisposing to CIED infection are presented in Supplementary material online, *Table S3*. Regarding host-related factors, the most significant predictors of infection included diabetes mellitus (OR = 2.08 [1.62–2.67]), end-stage renal disease (OR = 8.73 [3.42–22.31]), COPD (OR = 2.95 [1.78–4.90]), corticosteroid drug use (OR = 3.44 [1.62–7.32]), history of previous device infection (OR = 7.84 [1.94–31.60]), renal insufficiency (OR = 3.02 [1.38–6.64]), malignancy (OR = 2.23 [1.26–3.95]), and congestive heart failure (OR = 1.65 [1.14–2.39]) (*Figure 2*). Other significant host factors included New York Heart Association (NYHA) functional class ≥2, fever prior to implantation, oral anticoagulation, heparin bridging, and chronic skin disorders. Similar results were obtained in sensitivity analysis excluding studies with inadequate definition of infection (see Supplementary material online, *Table S4*). After exclusion of retrospective studies, few studies were available to be pooled in meaningful analyses. Nevertheless, diabetes mellitus, NYHA class ≥2, and pre-procedural fever remained significant predictors of infection, while COPD and skin disorders showed a trend towards increased risk for device infection (see Supplementary material online, *Table S5*).

Table 3 Variables identified as significant risk factors for CIED infection in at least two studies[a]

	Prospective studies (*n*)		Case–control studies (*n*)		Retrospective cohorts (*n*)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Host-related factors						
Age			1[11]		3[60,61,67]	3[14,60,67]
Male sex	1[37]		1[11]	1[11]	2[59,67]	1[67]
Diabetes mellitus			3[11,50,51]	1[50]	1[12]	1[12]
Renal insufficiency			2[11,51]	2[11,51]	1[75]	
ESRD/dialysis	1[47]	1[47]	1[15]		1[75]	
COPD	1[43]	1[43]	1[15]	1[15]	1[61]	
Anticoagulants	1[45]		2[11,51]	2[11,51]	1[60]	
Corticosteroids			1[16]	1[16]	1[60]	
CVC			1[16]		1[60]	1[60]
History of device infection			3[15,16,54]			
Implant site trauma			1[54]		1[63]	
Procedure-related factors						
Lack of antibiotic prophylaxis	7[28,30,31,33,34,40,42]	2[30,40]	1[16]	1[16]	3[60,67,70]	2[60,67]
Device replacement/revision	3[30,37,43]	2[40,43]	6[11,16,51–54]	3[11,51,53]	6[58,60,64,66,67,79]	2[60,79]
Reintervention	5[31,33,40,45,47]	2[40,47]	1[50]		1[71]	
No. of prior device-related procedures			2[15,16]		2[59,67]	1[67]
Temporary pacing	3[36,39,40]	1[40]	1[15]		1[71]	
Procedure duration	4[30,33,37,47]	1[47]				
Operator experience	1[33]		1[49]		1[55]	1[55]
Lead dislodgement	1[47]		1[53]			
Post-op haematoma	5[30,31,41,47,48]	1[30]	2[15,54]		1[60]	
Device-related factors						
ICD device	1[47]	1[47]			1[13]	
CRT					2[14,79]	2[14,79]
Dual-chamber system			2[50,54]	1[50]	1[67]	
No. of leads			1[16]	1[16]	1[14]	
Abdominal pocket	2[42,48]		1[52]		2[63,69]	
Epicardial leads			1[15]	1[15]	1[76]	

ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; No., number; Post-op, post-operative; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy.

[a]Characteristics that have been reported as risk factors for device infection only in one study: congestive heart failure,[11] malignancy,[16] skin disorders,[15] history of contralateral device implant,[45] elevated serum creatinine,[51] fever within 24 h before implantation,[40] dual/triple-chamber device,[53] duration of hospitalization (≥2 days),[15] Charlson index (≥4),[15] any post-operative complication,[15] heart disease, invasive procedure simultaneously with implantation,[50] use of drains,[65] the presence of subcutaneous defibrillation patch,[74] two-stage surgery, subcostal approach, decubitus ulcer,[63] screening time,[14] implantation during the first years of the study, procedural complexity, indication,[67] black race, cerebrovascular accident, gastrointestinal bleeding, dialysis modality, recent infection.[61]

Regarding procedure-related factors, post-operative haematoma (OR = 8.46 [4.01–17.86]), reintervention for lead dislodgement (OR = 6.37 [2.93–13.82]), device replacement/revision (OR = 1.98 [1.46–2.70]), lack of antibiotic prophylaxis (OR = 0.32 [0.18–0.55]), temporary pacing (OR = 2.31 [1.36–3.92]), generator change (OR = 1.74 [1.22–2.49]), inexperienced operator (OR = 2.85 [1.23–6.58]), and procedure duration (WMD = 9.89 [0.52–19.25]) were all significant predictors of CIED infection (*Figure 3*). When only studies with adequate definition were pooled, all the aforementioned factors but for procedure duration were still associated with higher infection rates. In prospective studies, device replacement/revision and generator change did not remain significant predictors of infection. Notably, in a separate analysis pooling data from randomized studies, lack of antibiotic prophylaxis was still associated with increased infection rates (OR = 0.26 [0.13–0.52]).

Among device-related characteristics, abdominal generator pocket (OR = 4.01 [2.48–6.49]), the presence of epicardial leads (OR = 8.09 [3.46–18.92]), positioning of two or more leads (OR = 2.02 [1.11–3.69]), and dual-chamber system (OR = 1.45 [1.02–2.05]) were predictors of CIED infection. Similar results were obtained in sensitivity analysis on the basis of definition. After pooling only prospective studies, abdominal pocket remained a significant risk factor for device infection, whereas dual-chamber system did not.

Assessment of publication bias is described in Supplementary material online, *Table S6*. Among factors associated with CIED infection in our meta-analysis, renal insufficiency, COPD, malignancy,

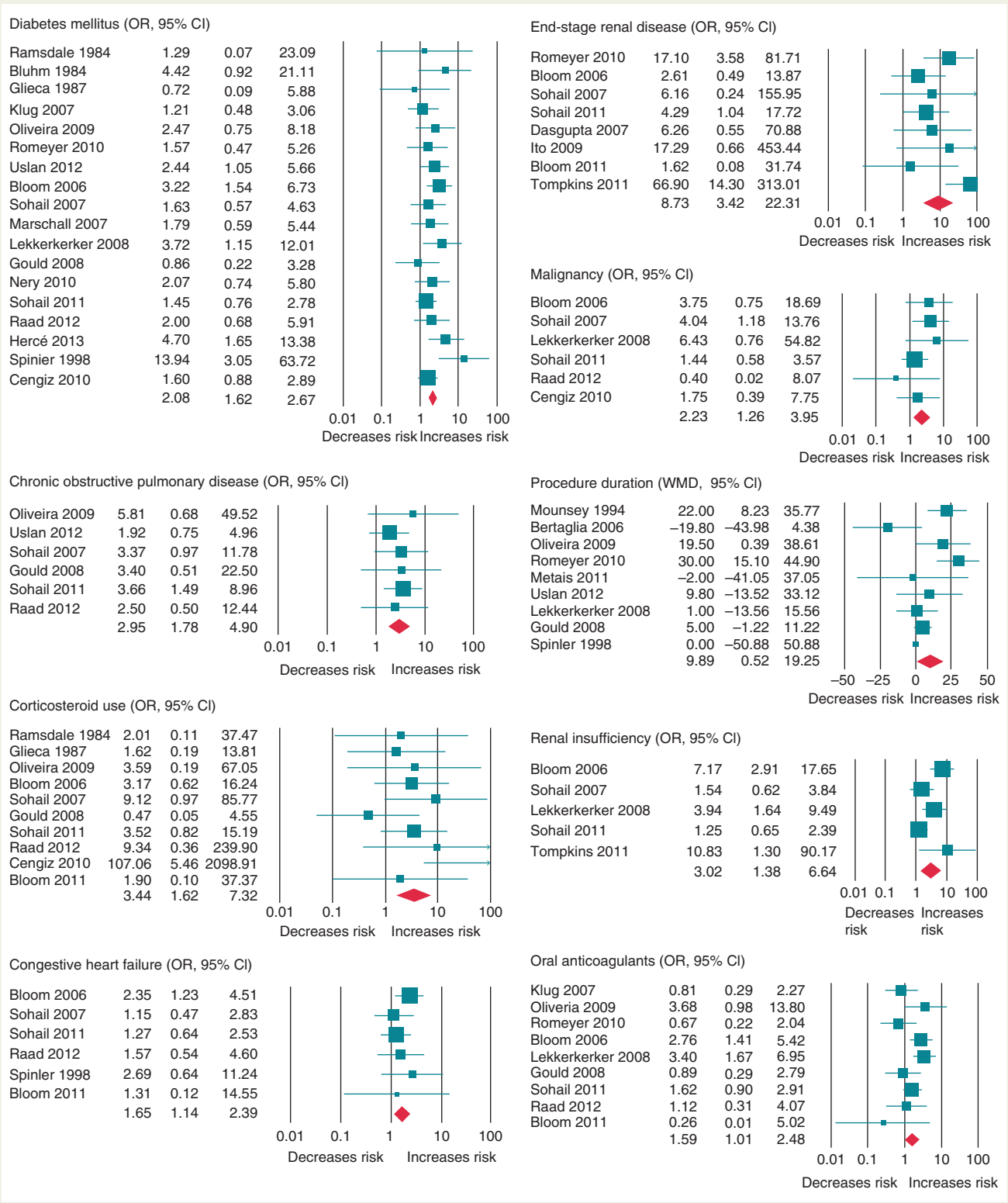

Figure 2 Forest plots for significant host-related risk factors for device-related infection with data available in at least five studies. *Squares*, odds ratios or weighted mean differences; *horizontal lines*, 95% CIs; *diamonds*, pooled odds ratios.

abdominal generator, dual-chamber device, and the presence of ≥2 leads showed slightly asymmetric funnel plots (data not shown). Egger's test for funnel plot asymmetry did not suggest the existence of publication bias for any of the aforementioned factors. Sensitivity analysis by the use of the trim and fill method did not affect the observed pooled estimates for renal insufficiency, COPD, malignancy,

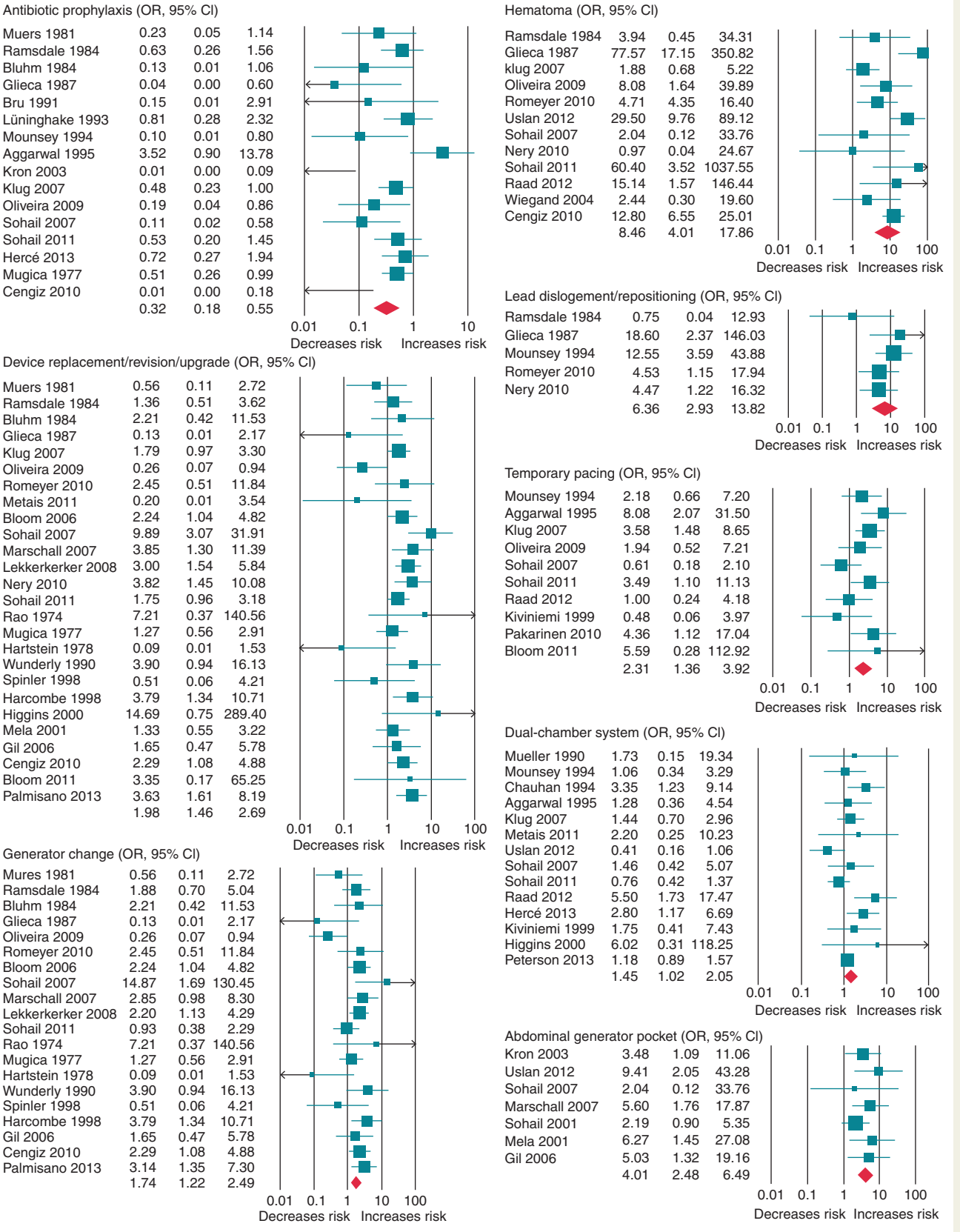

Figure 3 Forest plots for significant procedure- and device-related risk factors for device-related infection with data available in at least five studies. *Squares*, odds ratios or weighted mean differences; *horizontal lines*, 95% CIs; *diamonds*, pooled odds ratios.

and abdominal generator, but abolished the significant results for dual-chamber systems and number of leads. Regarding antibiotic prophylaxis, publication bias was suggested by funnel plots and Egger's test. However, the association between antibiotic prophylaxis and risk for infection remained significant in sensitivity analysis using Duval and Tweedie's trim and fill method.

Discussion

We systematically summarized the literature on potential risk factors for CIED infections. Among variables examined in at least five studies, significant host-related risk factors in our meta-analysis included diabetes mellitus, renal disease, COPD, corticosteroid use, malignancy, heart failure, and anticoagulant drug use. Procedure-related risk factors included lack of antibiotic prophylaxis, replacement/revision procedures, non-infectious post-operative complications (including lead dislodgement and haematoma), temporary pacing, and procedure duration. Regarding device characteristics, abdominal generator pocket, dual-chamber system, and positioning of two or more leads were identified as significant predictors of CIED infection.

Our results provide some insight into the increase in CIED infection rates reported over the past decade. Older age was not a significant predictor of device infection in our meta-analysis. It is most likely that an increase in the indications for CIED implantation in patients with serious comorbidities mostly accounts for the rise in the incidence infectious complications. Notably, ICD implantations in the USA increased by 504% between 1993 and 2008, whereas the respective increase in PPM implantations was only 45%.[2] In our analysis, ICD devices were not associated with higher infection rates. However, CRT had slightly higher risk for infection, which can be explained by the fact that these devices are often implanted in patients with more complex diseases, are more difficult to implant, and require longer procedure times.[82] Of note, almost half of the patients with heart failure and an indication for ICD implantation receive biventricular CRT devices.[83]

Apart from contributing to a better understanding of the epidemiology of CIED infection, the meta-analysis has also clinical relevance. The current recommendations on routine antibiotic prophylaxis at CIED implantation were largely based on a meta-analysis of randomized studies showing that antibiotics significantly reduce the risk for infective complications after PPM implantation.[10] Of note, the studies included in this analysis were conducted between 1976 and 1993, did not evaluate long-term infectious complications, and their quality could introduce bias (see Supplementary material online, *Table S7*). The effectiveness of antibiotic prophylaxis was later confirmed by a large prospective study in France.[40] Our meta-analysis, which included all interventional and observational studies to date with various durations of follow-up, confirmed the effectiveness of antibiotics to prevent infection in PPM, ICD, or CRT device recipients. Apart from systemic prophylaxis, antibiotic impregnated envelopes are now commercially available and have been suggested to reduce the risk for device infection in observational studies.[57,84,85]

Post-operative haematoma has been repeatedly associated with the risk for CIED infections and was a strong predictor of infection in our analysis. Therefore, particular attention should be paid on adequate haemostasis, especially in patients at high risk for perioperative bleeding. Oral anticoagulant use was significantly associated with CIED infection in our analysis, a finding that could be due to heparin bridging, which is normally used in clinical practice and has been linked with higher haematoma rates. Importantly, the American College of Chest Physicians recommends that patients with atrial fibrillation, mechanical valves, or venous thromboembolism at moderate-to-high risk for perioperative thromboembolism interrupt oral anticoagulation therapy and receive heparin bridging.[86] In this population, however, a recent randomized controlled trial showed that heparin bridging increased the incidence of pocket haematoma compared with continued warfarin treatment.[87]

Another clinically significant predictor of infection was device replacement, revision, or upgrade. This finding is of particular importance in the current era of frequent generator or lead advisories and recalls. In a multicentre cohort of patients undergoing advisory ICD replacement, the 12-month major infection rate was 2.2% while mortality rate was 0.4%.[49] A decision to replace a device should be made on a risk vs. benefit approach weighting the risk for death due to device failure, the rate of device failure, and the risk for procedure-related death.[88]

It should be mentioned that studies examining risk factors for infection in patients with blood stream infection were excluded from our analysis. These patients are more likely to develop CIED infection when bacteraemia is due to *S.aureus* (compared with Gram-negative micro-organisms) and when they are recipients of defibrillators (compared with pacemakers).[19] Notably, among patients with *S.aureus* bacteraemia the rate of CIED infection is ~36%, and significant predictors of device-related endocarditis include ICD device type and the presence of prosthetic valves.[89–91]

A number of limitations should be taken into consideration in the interpretation of our results. First, publication bias may have prevented us from identifying negative unpublished studies. To correct for this bias, we conducted sensitivity analysis using Duval and Tweedie's trim and fill method. Secondly, meta-analyses included mostly retrospective studies that varied in patient population, study quality, definition of infection, and follow-up, thus resulting in clinical and statistical heterogeneity in some of our analyses. Thirdly, the quality of the included studies was not systematically assessed. To address this issue, we performed sensitivity analyses on the basis of two aspects of methodological quality, design and adequate definition. These sensitivity analyses did not result in significant changes in the outcomes of the primary analyses. Finally, our pooled results were based on unadjusted effect estimates; the outcomes of multivariate analyses of individual studies are reported in the descriptive data synthesis.

Conclusions

In conclusion, this article summarized the medical literature on risk factors predisposing to cardiac device infections. This review will assist physicians in identifying patients at high risk for device infection after CIED implantation, and may also help risk assessment in the management of device revisions and recalls.

Supplementary material

Supplementary material is available at *Europace* online.

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