Infections of cardiac implantable electronic devices: Epidemiology, mechanisms, and preventive measures

Vassil Traykov[1], Krasimir Dzhinsov[2, 3], Paweł T Matusik[4, 5]

[1]Department of Invasive Electrophysiology, Clinic of Cardiology, Acibadem City Clinic University Hospital Tokuda, Sofia, Bulgaria
[2]Interventional Electrophysiology and Cardiac Pacing Unit, Interventional Cardiology Department, University Hospital "Sveti Georgi" — Plovdiv, Bulgaria
[3]Research Institute, Medical University — Plovdiv, Bulgaria
[4]Department of Electrocardiology, Institute of Cardiology, Faculty of Medicine, Jagiellonian University Medical College, Kraków, Poland
[5]Department of Electrocardiology, The John Paul II Hospital, Kraków, Poland

Correspondence to:
Vassil Traykov, MD, PhD, Clinic of Cardiology, Acibadem City Clinic Tokuda Hospital Sofia, Bulgaria, phone: +35 98 79 430 365, e-mail: vtraykov@yahoo.com

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ABSTRACT

Cardiac implantable electronic device (CIED) infections represent a complication associated with high morbidity and mortality. Despite enormous efforts to prevent them, the rates of infections continue to rise out of proportion to the reported increase in CIED implantation rates. Following extensive research of various prevention strategies and new technologies, several organizations have issued recommendations and consensus papers covering this topic. Our narrative review aims to provide a summary of the existing preventive strategies put forward by the European Heart Rhythm Association consensus and European Society of Cardiology guidelines and introduce the most recent developments in the field, including optimized surgical site management and appropriate periprocedural antithrombotic drug use. It also provides an overview of epidemiology, mechanisms, risk factors, and risk stratification approaches. It focuses on the pre-, intra-, and postprocedural actions that should be taken to mitigate CIED infection risks. Future directions in the prevention of CIED infections have also been addressed.

Key words: cardiac implantable electronic device, defibrillator, epidemiology pacemaker, infection, prevention, risk

INTRODUCTION

Following the first reports on cardiac pacemakers published in the late 1950s and the subsequent development of implantable cardioverter-defibrillators (ICD) in the 1980s, cardiac implantable electronic devices (CIEDs) have become the standard of care in managing cardiac rhythm and conduction disturbances. Published data show a constant increase in the numbers and complexity of CIED implantations worldwide [1]. This growth has been accompanied by an increasing rate of complications, especially with the wider introduction of cardiac resynchronization therapy pacemakers (CRT-P) and defibrillators (CRT-D) [2]. The rate of CIED infections has been shown to increase out of proportion to the reported rise in device implantation [1, 3]. The possible causes are the increasing CIED complexity, comorbidities, and longer life expectancy. On the other hand, CIED infections represent an essential factor for increased morbidity and mortality among CIED recipients [4]. From an economic perspective, CIED infection management puts a significant financial burden on healthcare systems due to additional treatment, prolonged hospital stays, and reinterventions [5–7].

Despite various preventive strategies to reduce CIED complications [8], reports show significant differences in their implementation [9]. Meticulous antisepsis and preoperative antibiotic prophylaxis are highly effective and recommended by various consensus papers and guidelines [8, 10]. New technologies, including subcutaneous ICDs and leadless pacemakers, also aid in the reduction in CIED infections. However, these apply only to selected patients. The role of antibiotic-eluting envelopes (AEEs) for effective CIED infection prevention has been demonstrated by randomized studies [11].

Moreover, advances in diagnostics, including use of procalcitonin in the recognition of device pocket infection, have been done recently [12].

This narrative review presents an overview of the epidemiology and mechanisms of CIED infections as well as the existing and developing strategies to prevent them. It highlights the strategies for risk stratification and focuses on the value of preprocedural, intraprocedural, and postprocedural measures and actions to prevent CIED infections.

EPIDEMIOLOGY, ETIOLOGY, AND MECHANISMS OF CIED INFECTIONS

Infections related to the CIED develop at a rate ranging from 1 to 7% depending on the type and complexity of the implantation [2, 6, 11, 13]. Previously reported data demonstrated a significant rise in the infection rates over time from 1.45% to 3.41%, with the highest increase for CRT-P/D devices [1]. Real-life data on infection rates contrast with results from randomized studies, which report much lower infection rates in the range of 0.6%–1.3% [4, 11, 13–15]. This could result, at least in part, from predominant participation of high-volume centers in randomized studies. The infection rate is highest early after the procedure (in the first 3 months) [16]. Infections are well-known to be associated with increased morbidity and mortality, especially in the case of systemic and delayed (3–12 months) localized infections [4, 16, 17]. This trend is preserved even after lead extraction (complete CIED removal) [4] and successful infection eradication [17].

CIED infections develop via two major mechanisms. The most common is local hardware (leads and pulse generator) contamination [18]. The introduction of normal skin flora might occur in the surgical wound during the implantation or later with the development of erosion. Contamination of the pocket leads to bacterial growth and subsequent (mostly early) pocket infection [11, 19, 20]. Later in its course, the infection may spread along the leads and eventually cause secondary systemic infection resulting in device-related endocarditis. In the second mechanism, remote infectious foci (e.g., from contaminated vascular catheters, surgical site infection, septic thrombophlebitis, etc.) causing bacteremia might result in direct lead seeding, which later may progress to systemic infection, while the device pocket remains unaffected.

Device infections are caused mainly by Gram-positive bacteria (70%–90% of the isolates). Some of them are normally non-pathogenic. These are usually coagulase-negative staphylococci (mainly *Staphylococcus epidermidis*). *Staphylococcus aureus* is also a commonly isolated microorganism responsible for pocket infection (especially in early cases) and also the most common isolate in bacteremia [21–26]. Almost half of all staphylococcal CIED infections have been reported to be caused by methicillin-resistant staphylococci [21]. Gram-negative bacteria are isolated in about 9% of the cases, while fungi are rare [25]. No causative microorganism is identified in about a third of the patients [11].

RISK ASSESSMENT

Any preventive measure shows the highest benefit when directed to the population at the highest risk. Identifying risk factors and risk stratification play a central role in determining the CIED recipients for whom more aggressive preventive measures should be taken to reduce the infection rate.

Factors associated with higher CIED infection risk can be modifiable, with specific interventions addressing them able to mitigate the risk, or non-modifiable, determining persistently elevated risk of infection. Apart from that, risk factors can be grouped into patient-related, procedure-

Table 1. Major risk factors for cardiac implantable electronic device infections

Risk factors	Odds ratio
Patient-related factors	
End-stage renal disease	8.73
Prior CIED infection	7.84
Fever before implantation	4.27
Immunosuppression	3.44
Renal failure (eGFR <30 ml/min/1.73 m^2)[a]	1.45[a]–3.02
COPD	2.95
NYHA class ≥II	2.47
Skin disorder	2.46
Immunocompromised (therapy or disease-suppressing resistance to infection)	2.28[a]
Malignancy	2.23
Diabetes mellitus	2.08
Heparin bridging	1.87
Congestive heart failure	1.65
Oral anticoagulation	1.59
Device-related factors	
Epicardial leads	8.09
Abdominal pocket	4.01
CRT	2.73[a]
Two or more leads	2.02
ICD	1.77[a]
Dual chamber device	1.45
Procedure-related factors	
Reintervention <30 days	16.29
Procedure duration > 1 hour	13.96
Hematoma	4.95-11.3[b]
Revision or upgrade	4.01[a]–6.46
Lead repositioning	6.37
Replacement	4.93
Two or more prior procedures	3.43[a]
Inexperienced operator	2.85
Temporary pacing	2.31
Single prior procedure	1.51[a] (P = 0.058)[a]

Abbreviations: CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; CRT cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; h, hour; ICD, implantable cardioverter-defibrillator

Data marked with an asterisk or paragraph sign come from randomized controlled trials

Figures taken from previously published non-randomized data by Polyzos et al. [27], Sławek-Szmyt et al. [28], and from randomized data by Birnie et al.([a]) [29] and Tarakji et al. ([b]) [32]

-related, and device-related [8]. The magnitude of different risk factors is presented in Table 1.

PATIENT-RELATED RISK FACTORS

Some comorbidities are well-established risk factors. End-stage renal disease and renal insufficiency or failure are consistently reported as one of the most important risk factors [14, 27, 28]. Other conditions such as immunosuppression, chronic obstructive pulmonary disease (COPD), congestive heart failure, valvular heart disease (esp. prior valvular surgery), systemic autoimmune disorders, malignancy, diabetes, and skin disorders also carry a significant risk of CIED infection [15, 27–29]. Although often non-modifiable as risk factors, optimal management of these conditions (e.g., control of diabetes) has been shown to lower infection risk [30].

Younger age has been identified as a risk factor in the randomized Prevention of Arrhythmia Device Infection Trial (PADIT) population and by a recent large observational study [15, 29]. While a consistent explanation for this finding is lacking, the qualities of subcutaneous tissue at a younger age might predispose to more traumatization during implantation (esp. pocket creation) and subsequent higher predisposition to infection [31]. Conversely, a smaller observational study including only 1000 ICD and CRT recipients demonstrated a significantly higher risk of CIED infection (odds ratio [OR], 5.93; 95% confidence interval [CI], 1.77–19.84) in patients older than 75 years [28]. This might be due to the inclusion of more frail and morbid patients in this series.

Fever before implantation is another well-established and major modifiable risk factor for CIED infection (OR, 5.34; 95% CI,1.002–28.43) [8]. The administration of certain medications, such as corticosteroids and antithrombotic drugs, also represents a potentially modifiable patient-related risk factor. According to a recent analysis of randomized data, a history of atrial arrhythmia and the number of previous procedures were also associated with increased infection risk after secondary procedures [32]. In the same study, some geographical regions (outside North America and Europe) and lower body mass index were also associated with increased risk.

DEVICE-RELATED FACTORS

Device-related factors mainly include system size and complexity. Implantation of complex systems, presence of at least two leads, and implantation of high-power devices are associated with increased infection risk [8, 27, 33–35] (Table 1). A sizeable real-life registry from Denmark reported significantly increased infection risk in patients with complex devices — ICD (HR, 1.26, 95% CI, 1.09–1.47), CRT-P (HR, 1.68; 95% CI, 1.67–2.11), and CRT-D systems (HR, 2.22; 95% CI, 1.83–2.70) as compared to conventional antibradycardia devices [35]. Another, more recent analysis of data from the same registry reported that complex systems (CRT-P and CRT-D) are associated with increased risk for both pocket and systemic CIED infections, while ICD implantation portended a higher risk of systemic infection compared to implantation of antibradycardia pacemakers [15]. In the PADIT study population, implantation of CRT and ICD, as well as secondary procedures, were all associated with increased risk for CIED infection in a full prediction model (OR, 2.73; 95% CI, 1.72–4.31; OR, 1.77; 95% CI, 1.09–2.87 and OR, 4.01; 95% CI, 2.62–6.13, for CRT, ICD, and secondary procedures, respectively) [14]. Similar findings were reported in the WRAP-IT dataset as well [32].

PROCEDURE-RELATED RISK FACTORS

Previously published observational and randomized studies demonstrated that early reintervention (within 30 days) and lengthy procedure duration (> 1 hour) were associated with the highest risk of CIED infections [8, 27, 32–34]. Procedure duration is mainly affected by procedure complexity, patients' anatomy, and operator skills and experience.

Postprocedural hematoma is another well-established risk factor that has been widely studied. The randomized BRUISE CONTROL INFECTION study, including 659 patients with CIED infection, demonstrated that the development of hematoma was associated with more than 7-fold increased risk of infection (hazard ratio [HR], 7.7; 95% CI, 2.9–20.5) within one-year follow-up [33]. Another recent analysis based on the WRAP-IT population (n = 6800 participants) demonstrated an 11-fold increase in CIED infection risk (HR, 11.3; 95% CI, 5.5–23.2) in the patients developing clinically significant hematoma [34].

RISK SCORES

Risk score systems for preprocedural risk assessment represent an essential tool for better risk stratification of low- and high-risk patients. They can not only facilitate clinical decision-making and patient counseling but also help healthcare systems and decision-makers be prepared for the scale of these severe complications. Mittal et al. [36] were among the first to develop a risk scoring system that included 7 clinical variables and 0 to 25 points (a higher number signifying higher risk). The infection risk increased significantly from the low-risk group (score 0-7, 1% infection rate) to the medium-risk group (score 8–14, 3.4% infection rate), and the high-risk group (score ≥15, 11.1% infection rate). Shariff et al. [37] also proposed a risk score including ten clinical and procedural variables. In a retrospective study, in patients who underwent *de novo* CIED implantation, Shariff score ≥4 was associated with more than three-fold increased risk of CIED infection — RR 3.20 (1.29–12.59) [38]. Another risk score designed by Kolek et al. included several clinical variables also known to be associated with CIED infection risk [39, 40]. The only risk score developed based on a dataset of a randomized trial is the PADIT risk score system [29]. It identified five independent predictors: Prior procedure(s) (P, 1 = 1 point, at least 2 = 4 points), Age (A, 60–69 years = 1 point, <60 years = 2 points), Depressed estimated glomerular

filtration rate (D, <30 ml/min = 1 point), Immunocompromised (I, 3 points), and Type of procedure (T, ICD = 2 points, CRT = 4 points, revision or upgrade = 5 points). The score, ranging from 0 to 15 points, was used to group patients into low (<1%, 0 to 4 points), intermediate (1%–3%, 5 to 6 points), and high (>3%, ≥7 points) risk groups with hospitalization rates due to CIED infection of 0.51%, 1.42%, and 3.41%, respectively. The PADIT risk score was validated externally in a large dataset of 54 042 procedures where each unit increase in the PADIT risk score was associated with a 28% increase in the infection risk [41]. Following PADIT risk score development, Boriani et al. [42] developed the RI-AIAC infection score based on registry data with 2675 patients. The RI-AIAC score is a 5-point scoring system, and the authors have identified several major clinical characteristics associated with increased CIED infection risk (especially type of procedure and diabetes). Interestingly, a score created to assess the risk of bleeding complications in CIED recipients — the PACE DRAP score — has also been shown to be helpful in CIED infection risk stratification [28]. It is important to note that none of these risk scores are entirely exhaustive. For instance, the most widely used PADIT risk score does not include important risk factors such as prior CIED infection, some comorbidities (e.g. malignancy), and concomitant antithrombotic therapy. Real-life studies have shown that previous CIED infection remains an important risk factor despite adjustment for the PADIT risk score [41].

PREVENTION STRATEGIES

Infections associated with CIEDs represent a significant challenge for healthcare providers and systems. Therefore, prevention is essential to reduce their incidence and diminish mortality and morbidity associated with them. In the case of CIED infection, preventive strategies include multiple measures at different time points during the management of these patients – before, during, and immediately after the implantation [8].

PREPROCEDURAL MEASURES

Patient selection and preprocedural patient-related factors

Careful patient selection and procedure timing are essential in CIED infection prevention. The risk-benefit ratio should always be considered individually before the procedure, with strict adherence to the recommendations [10]. For instance, a significant proportion (up to 50%) of patients might not need reimplantation of a new device following extraction for CIED infection [43-45]. Cardioneuroablation, as a new treatment modality for vasovagal syncope, is also likely to make implantation in some patients obsolete [46]. Careful consideration of temporal variation in the risk and postponing an implantation/reimplantation procedure to gain time to implement preventive measures play a central role in the decision-making process [47].

Preprocedural fever is a factor that necessitates postponing the procedure. As suggested by the available data, a reasonable afebrile period before undertaking the implantation procedure is at least 24 hours [48]. Isolated leucocytosis, without other clinical symptoms and signs (bacteremia, elevated inflammatory biomarkers) of ongoing infection, has not been associated with CIED infections and should not delay implantation [49]. Optimizing treatment and better control of comorbidities (e.g., better glycemic control in diabetic patients) is very important to minimize the risk of CIED infections.

Some studies have demonstrated the benefit of identifying *S. aureus* carriers by nasal swabs and subsequent decolonization with topical mupirocin and chlorhexidine skin wash to reduce healthcare-associated *S. aureus* infections [50]. Whether this strategy would prove beneficial in reducing CIED-related infections has not been specifically studied.

Implantation of temporary pacing leads should be avoided to reduce the risk of CIED infection. Alternative solutions, such as considering transcutaneous pacing in the most severe cases or administering medications to increase heart rate, should be sought and implemented. When needed, temporary transvenous pacing is better carried out via jugular/subclavian access rather than groin access, as this may be associated with lower infection risk. If possible, removing all central venous lines should be considered before CIED surgery [27]. In the case when vascular access was via a subclavian vein, the CIED should be implanted on the contralateral side. If that is not possible or feasible, it is always advisable to postpone the implantation after removing the central venous line.

If hair removal at the procedural site is needed, this should be done using electric clippers with a disposable head (not razors) [51]. Preprocedural skin wash with an antimicrobial agent is not routinely recommended due to diverging data from studies on other types of surgery and not specifically CIED implantation [8].

Antithrombotic therapy

Patients undergoing CIED implantation frequently need concomitant antiplatelet or anticoagulant therapy. As shown above, postoperative hematoma is a decisive risk factor for CIED infection; therefore, every effort should be made to minimize the risk of hematoma formation. One widely implemented strategy is uninterrupted vitamin K antagonist (VKA) therapy during implantation [52]. The Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE-CONTROL) demonstrated that uninterrupted VKA therapy, as compared to heparin bridging, resulted in fewer clinically significant device-pocket hematomas as compared to a strategy involving perioperative VKA interruption and bridging with heparin in patients with high thromboembolic risk (including patients after mechanical heart valve replacement) 3.5 vs. 16% (RR, 0.19; 95% CI, 0.10–0.36) [53]. The ran-

domized BRUISE CONTROL-2 study found no difference in the clinically significant device pocket hematoma incidence with continued direct oral anticoagulants (DOAC) therapy vs. DOAC interruption in patients with atrial fibrillation and CHA_2DS_2-VASc score ≥2 [54]. A combined analysis of these two trials also demonstrated similar bleeding and pocket hematoma outcomes between interrupted or continued DOAC therapy vs. uninterrupted VKA (OR, 0.86; 95% CI, 0.38–1.96) [55]. In patients with low thromboembolic risk, temporary withholding of oral anticoagulation for the implantation is a well-established strategy [8].

Concomitant single or dual antiplatelet therapy increases bleeding risk in CIED recipients [56, 57]. Analyses of randomized studies demonstrated that a clinically significant hematoma develops in 9.8% of the patients on concomitant antiplatelet therapy versus 4.3% in those without, corresponding to a doubling of the risk (OR, 1.97; 95% CI, 1.20–3.21) [55]. Therefore, recent guidelines and consensus documents recommend discontinuing antiplatelet therapy (especially $P2Y_{12}$ inhibitors) for at least 5 days before the procedure, if possible [8, 10]. In patients on dual antiplatelet therapy following percutaneous coronary intervention (PCI), discontinuation of one of the antiplatelet agents (usually $P2Y_{12}$ inhibitor) for 3–7 days before the procedure is recommended based on thromboembolic and bleeding risk [10].

Antibiotic prophylaxis

Previous studies have demonstrated a significant and considerable reduction in the incidence of CIED infection with preprocedural intravenous antibiotic prophylaxis [58, 59]. In the randomized trial of de Oliveira et al., preprocedural administration of 1 g cefazolin was associated with a significant reduction in infection rates as compared to placebo (0.63% vs. 3.28%; RR, 0.19; $P = 0.016$) [59]. Current guidelines recommend such a strategy as the standard of care [8, 10]. Antibiotics should protect against *S. aureus* as the most common causative organism in acute infections. Randomized trials have used flucloxacillin (1–2 g) and first-generation cephalosporins — e.g., cefazolin (1–2 g) [14, 59]. In cases of allergy to beta-lactams, the recommended choice is vancomycin (15 mg/kg) [8]. Antibiotics against methicillin-resistant *S. aureus* (MRSA) are not used routinely and could be considered based on local MRSA prevalence and patient risk. Antibiotic administration should be completed within one hour before the skin incision to ensure adequate antibiotic tissue levels.

Alternative systems and approaches in high-risk patients

The development of technology has brought in leadless pacemakers and subcutaneous ICD as an alternative to conventional transvenous systems. As these devices have no or only minimal intravascular components, they are expected to be associated with lower risk of infection. The absence of a pocket in leadless pacemakers eliminates the risk of CIED pocket infection although hematogenous seeding might still be possible. Extensive observational studies report a significantly lower infection rate with this new technology, but results from randomized studies are lacking [60]. Leadless pacemakers may also be associated with reduced risk of infection in patients after transvenous lead extraction [61]. High costs and lack of reimbursement are among the factors limiting their use in clinical practice. However, when considering total costs for the management of patients with recurrent CIED infections, leadless pacemaker implantation seems to be financially justified, at least in some healthcare systems [62].

Subcutaneous ICDs (S-ICD) are a viable option for patients requiring protection from ventricular tachyarrhythmias and have no pacing or CRT indication. Results from the EFFORTLESS S-ICD registry showed that at five years of follow-up, the overall infection rate in S-ICD recipients was 2.4% with an erosion rate of 1.7% [63]. A recent secondary analysis of the PRAETORIAN trial demonstrated a significantly lower rate of systemic infections in S-ICD recipients than those receiving a transvenous ICD (0% vs. 1.2%) [64].

Implanting an epicardial system may also provide a solution in selected high-risk patients, particularly those in whom preserving venous access is crucial [65].

Other preprocedural measures

An appropriate environment in the operating room/catheterization laboratory where CIED implantations are carried out is essential. These facilities should meet all the standards applicable for other surgical procedures involving implants [8, 66]. The staff at the implantation facility should be trained to follow strict sterile techniques.

Procedure times should be minimized as the duration of the implantation is a well-established risk factor for CIED infection. Long procedures (>60 minutes) are associated with infectious complications [27]. Extensive real-life data have demonstrated that, compared to procedure durations up to 30 minutes, the risk of infections is 2.4-fold higher in procedures longer than 120 minutes [35]. Many factors have an impact on procedure duration. Among those are lack of appropriate staff training [67], certification of operators [68], and patient volume [69]. These are all organizational issues that should be best addressed before starting any activity i.e., before performing any procedures. However, procedural difficulties associated with patient-related factors, e.g. anatomical/structural abnormalities/changes or bleeding, also play a role in procedural duration.

SURGICAL TECHNIQUE AND INTRAPROCEDURAL FACTORS

Surgical preparation

Results from randomized trials demonstrated that skin antisepsis with a 2% alcoholic chlorhexidine solution was associated with a lower incidence of surgical site infections as compared to povidone-iodine (alcoholic or aqueous

solution) [70]. It is also associated with a lower infection rate with intravascular catheter insertion [71]. Despite the lack of randomized data on CIED implantation, the use of alcoholic chlorhexidine is recommended [8]. To provide sufficient time for the antiseptic to exert its effect and to minimize fire hazards when using electrocautery, it should be left to dry completely before the incision is made. Many operators use iodophor-impregnated incisive drapes, but there are no data showing that they reduce infection rates [9].

Surgical technique

Good surgical techniques including minimizing operative tissue damage, meticulous hemostasis, and appropriate wound closure, are crucial elements in infection prevention during the CIED implantation procedure.

Gloves change

Many operators change their gloves initially during prepping and/or later before handling the device. This is usually done by removing the outer pair of gloves with double-gloving or re-scrubbing. Observational studies have shown a high rate of glove contamination during the implantation before handling the device [72]. As significant, randomized studies in the field are lacking, the practice of glove change has been recommended based on expert consensus. The use of non-powdered gloves is preferable because glove powder has been demonstrated to facilitate infection [73].

Hemostasis and prevention of hematoma

Adequate hemostasis is key in the prevention of hematoma formation. Minimizing trauma by respecting tissue architecture and ensuring good wound closure is extremely important. Electrocautery is widely implemented in most centers, but the use of a plasma electron avalanche knife has been shown to be associated with a reduced incidence of hematoma compared to electrocautery in high-risk patients [74]. Some observational studies advocate for the use of hemostatic agents such as tranexamic acid [75]. However, results are controversial, and therefore this strategy cannot be recommended as a standard practice until larger-scale studies demonstrate its unequivocal benefit and safety. Routine addition of epinephrine to the local anesthetic during the procedure is discouraged as one small randomized single-center study demonstrated a higher incidence of hematoma formation with this strategy [76]. Capsulectomy entails the removal of the fibrous capsule formed around the device during secondary procedures. The rationale behind this practice is that the fibrous capsule has been known to facilitate bacterial colonization and subsequent infection. A randomized study demonstrated that routine capsulectomy during secondary procedures results in more hemorrhagic complications (6.1% vs. 0.8%; $P = 0.03$) with no effect on the incidence of pocket infection (1.5% vs. 4.7%; $P = 0.13$) [77]. Therefore, performing capsulectomy on a routine basis is discouraged.

Pocket irrigation and local instillation of antibiotics and antiseptics

The PADIT trial demonstrated no difference in the infection rate with the application of incremental antibiotic strategy, including antibiotic pocket wash before skin closure along with postoperative cephalexin or cephadroxil as compared to preprocedural cefazolin infusion only [14]. The recent Randomized Stand-Alone Use of the Antimicrobial Envelope in High-Risk Cardiac Device Patients (ENVELOPE) trial showed no difference in infection rates in high-risk patients receiving chlorhexidine skin preparation, preprocedural antibiotics, and an AEE (control arm) compared to adding an antibiotic pocket wash and a 3-day course of postoperative antibiotics to the initial treatment [13]. Observational studies do not support performing routine povidone-iodine pocket irrigation to reduce infection rates [78]. Based on these data, local instillation with antibiotics or antiseptic solutions is not recommended [8]. However, gentamicin-impregnated collagen sponge use was associated with reduced CIED infections in a recent 10-year analysis with propensity score matching [79]. In all cases, vigorous pocket irrigation with saline should be done to remove debris and potential contaminants from the pocket during the implantation.

Antibiotic eluting envelopes

In their early versions, AEEs consisted of non-absorbable polypropylene mesh, but this design was associated with significant pocket fibrosis and was therefore abandoned. An antibacterial mesh envelope has been designed and marketed (TYRX™; Medtronic, Inc. Monmouth Junction, NJ, US). It is made of a synthetic mesh of glycolide, caprolactone, and trimethylene carbonate absorbed in the body over nine weeks. The mesh is coated with an absorbable polyacrylate polymer releasing minocycline and rifampin in the tissues over seven days. This antibiotic combination has been shown to have additive effects on resistant bacteria such as MRSA [80] and covers the whole spectrum of Staphylococcus spp. (81), as well as other species [82].

The randomized WRAP-IT trial assessed AEE benefits in patients undergoing device implantations. It included 6983 patients with high infection risk randomized to AEE vs. standard of care [82]. Major infections occurred in 0.7% of patients receiving TYRX™ vs. 1.2% in controls (HR, 0.60; 95% CI, 0.36–0.98) [11]. The positive outcome was entirely driven by the lower rate of pocket infections, which comprised 75% of all major events — 0.4% vs. 1% in the control group (HR, 0.39; 95% CI, 0.21–0.72). The benefit of AEE was sustained during long-term follow-up [83]. A meta-analysis summarizing a major observational and randomized trials and a recent real-world study demonstrated similar findings [84, 85]. Further analyses of the WRAP-IT population showed a more than 11-fold higher risk of major CIED infection in patients with pocket hematoma and without the AEE [34]. In patients who received the AEE and later developed pocket hematoma, the risk was 82% lower (HR, 0.18; 95% CI,

0.04–0.85), and the infection rate was comparable to those without hematoma. A significant limitation of the study was the exclusion of patients at very high risk (e.g., those with pocket intervention in the previous 365 days, patients on dialysis, on chronic immunosuppressive therapy, or those with previous CIED infection within 12 months), which probably explains the lower than expected infection rate. The cost-effectiveness of this device, especially in high-risk patients, has been demonstrated in many healthcare systems [86–89].

Another available absorbable CIED envelope is made of a decellularized and non-crosslinked extracellular matrix produced from porcine intestinal submucosa [90]. This envelope does not possess antibiotic-eluting properties *per se* but can be impregnated with gentamycin before implantation [90, 91]. Before recommending this envelope for routine clinical use, results from ongoing randomized trials are awaited.

Wound closure

Adequate wound closure is of paramount importance to prevent pocket infections. Closure in layers has been shown to reduce the risk of dehiscence [92]. Various suture materials, staples, or adhesives may be used for wound closure. However, it is extremely important to ensure timely (within 7–14 days) removal of non-absorbable suture material. No firm data have demonstrated the impact of suture material on the infection risk, but consensus documents recommend the use of non-braided monofilament sutures for skin closure as they may be less prone to bacterial adhesion [8]. With absorbable sutures, care should be taken to avoid a "stitch abscess", especially at the pole of the wound where the knot is located.

POSTPROCEDURAL MEASURES

Postprocedural antibiotic therapy

Postoperative antibiotic therapy is not recommended based on the results of the large PADIT trial. The trial tested the benefit of incremental perioperative antibiotic therapy to reduce CIED infections in a cluster cross-over design. In 19 603 patients (of whom 12 842 were high risk), the authors did not find a significant reduction in infections in the patients treated with an incremental regimen consisting of preprocedural cefazolin plus vancomycin, bacitracin pocket wash, and postoperative 2-day administration of oral cephalexin (OR, 0.77; 95% CI, 0.56–1.05) [14]. However, incremental antibiotic use compared to standard care was associated with a trend toward a 23% reduction in hospitalization for infection. This finding was not significant, at least in part due to the low infection rate during only 1-year follow-up in the PADIT trial [29]. Similarly, the recent ENVELOPE trial did not find an additional benefit of antibiotic pocket wash and a 3-day postoperative antibiotic course in addition to standard care and an AEE in high-risk CIED patients [13]. These results should be interpreted in light of the low incidence of CIED infections with peri- and post-operative antibiotic use (course of 5 days) in the long-term follow-up [93].

Wound care

Mechanical compression devices have also been designed to be applied after wound closure. Some of these devices have demonstrated benefit in reducing postoperative hematoma [94–96]. Pressure dressings may be used for 24 hours although their efficacy has not been demonstrated. In any case, a sterile dressing should be left on the wound for 2–10 days, and patients should be given instructions for wound care, i.e., changing the dressing only if impregnated with blood or wound secretions and not soaking the wound until completely healed [8].

Reintervention

Some procedure-related complications (lead dislodgement, hematoma, etc.) may require reintervention. Proper timing is crucial in these cases as the infection risk of repeat procedures is time-dependent and very high in early reinterventions [27, 48]. As shown by the Prospective Evaluation of Pacemaker Lead Endocarditis (PEOPLE) study, reinterventions before hospital discharge are associated with 15-fold increased risk of CIED infection [48]. Apart from taking all the measures to avoid the need for repeat procedures (meticulous hemostasis, good lead fixation, etc.), careful consideration of the risks and benefits of early reintervention is extremely important.

The most important risk factors and major risk reduction strategies are summarized in Figure 1.

FUTURE DIRECTIONS

There are several gaps in evidence related to CIED infection prevention that require further study to answer important questions in the field. More studies on nasal and/or skin treatment of bacterial decolonization to prevent CIED infections would be valuable, especially in high-risk patients. Randomized studies on skin preparation before CIED placement and use of adhesive incise drapes are eagerly awaited. Studies on the use of antiseptic/antimicrobial solutions (e.g. taurolidine) for pocket and hardware wash are ongoing (NCT05576194), but large, randomized trials are needed. Investigations onto different approaches expected to increase guideline-driven care for patients with CIED infections are ongoing (NCT05471973).

CONCLUSION

As a result of increasing device complexity and more prevalent comorbidities in patients undergoing CIED placement, the incidence of CIED infections has grown significantly. They are associated with high morbidity and mortality, as well as high healthcare costs for hospital stay, diagnostics, medical therapy, and interventional (or surgical) procedures. Therefore, identifying risk factors is crucial for implementing structured prevention measures

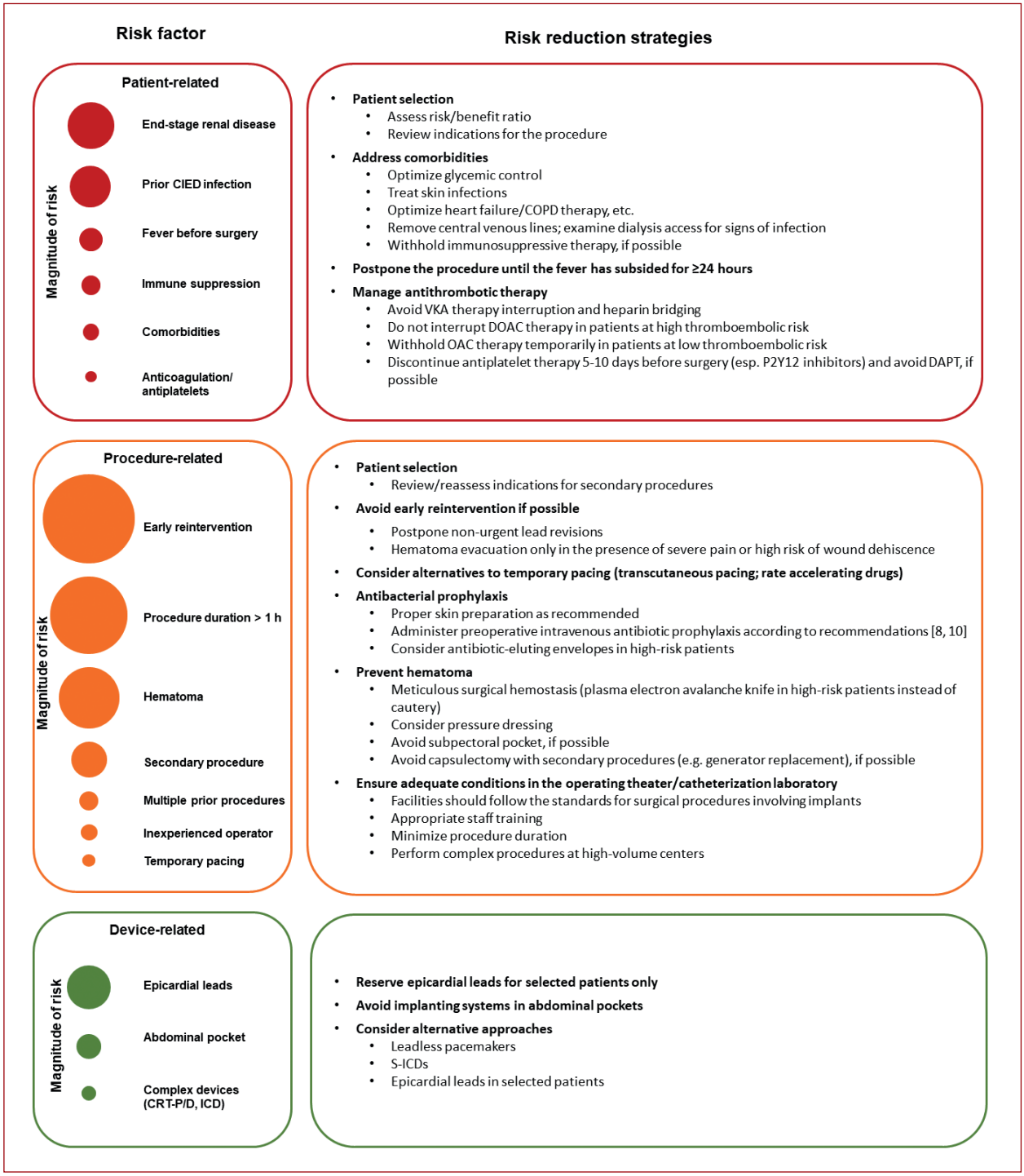

Figure 1. The most important risk factors of cardiovascular implantable electronic device infections along with the corresponding strategies to mitigate that risk. Colored circles reflect the magnitude of risk based on the results presented in Table 1

and actions at the preprocedural, intraprocedural, and postprocedural levels, which could bring about a meaningful reduction in CIED infection incidence. These actions should target patients and procedures but also should be directed to the environment in the operating room, staff training, and institutional measures. Importantly, studying and incorporating new methods and technologies such as AEEs, leadless pacemakers, and S-ICDs is another action to be taken for more effective prevention of CIED infections.

Article information

Conflict of interest: VT declares receiving speaker fees and other honoraria from Boehringer Ingelheim, Astra Zeneca, Berlin Menarini, Abbott, Novartis, Bayer, Merck, Pfizer, and Biotronik. KD declares receiving speaker fees from Sandoz, Servier, Boehringer Ingelheim, Astra Zeneca, Berlin-Chemie/Menarini, Novartis, Bayer, Pfizer, and Medtronic. PTM received speech honorarium from Boehringer Ingelheim, Polish Cardiac Society 2018 Scientific Grant in cooperation with Berlin-Chemie/Menarini (sponsor of the grant: Berlin-Chemie/Menarini Poland LLC) and participated in educational activities which were supported by CIED manufacturers as well as Polpharma. None of the declared conflicts are related to the current work.

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