Antibiotic prophylaxis based on individual infective risk stratification in cardiac implantable electronic device: the PRACTICE study

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Aims
In patients undergoing cardiac implantable electronic device (CIED) intervention, routine pre-procedure antibiotic prophylaxis is recommended. A more powerful antibiotic protocol has been suggested in patients at high risk of infection. Stratification of individual infective risk could guide the prophylaxis before CIED procedure.

Methods and results
Patients undergoing CIED surgery were stratified according to the Shariff score in low and high infective risk. Patients in the ‘low-risk’ group were treated with only two antibiotic administrations while patients in the ‘high-risk’ group were treated with a prolonged 9-day protocol, according to renal function and allergies. We followed-up patients for 250 days with clinical outpatient visit and electronic control of the CIED. As primary endpoint, we evaluated CIED-related infections. A total of 937 consecutive patients were enrolled, of whom 735 were stratified in the ‘low-risk’ group and 202 in the ‘high-risk’ group. Despite different risk profiles, CIED-related infection rate at 250 days was similar in the two groups (8/735 in ‘low risk’ vs. 4/202 in ‘high risk’, \(P = 0.32\)). At multivariate analysis, active neoplasia, haematoma, and reintervention were independently associated with CIED-related infection (HR 5.54, 10.77, and 12.15, respectively).

Conclusion
In a large cohort of patients undergoing CIED procedure, an antibiotic prophylaxis based on individual stratification of infective risk resulted in similar rate of infection between groups at high and low risk of CIED-related infection.

Keywords
Cardiac implantable electronic device • Infection • Antibiotic prophylaxis • Pacemaker • Implantable cardioverter-defibrillator • Shariff score

Introduction
Cardiac implantable electronic devices (CIED), namely pacemakers and implantable cardioverter-defibrillators (ICD) including cardiac resynchronization therapy (CRT) devices, are commonly used for the treatment of brady-arrhythmias, tachy-arrhythmias, and chronic heart failure. Infections of CIED are important complications with an incidence of ~1–3% during lifetime, variable according to patient, operator, and device characteristics.1–3 Unfortunately, large cohort studies showed that infections increase over time impacting negatively on CIED prognosis.1,2 Infective process can affect subcutaneous device pocket, intravascular lead, or both.

A great number of risk factors for CIED infections have been identified and may be divided whether they relate to patient, procedure,
or device. From a practical point of view, a pre-operative rapid assessment of individual infective risk can be obtained with a simple score, originally proposed by Shariff et al. The Shariff score was tested in a retrospective large cohort of patients with a median follow-up of 48 months: a score >3 at first implantation was an independent predictor of CIED infection while a score = 3 reached borderline significance.

Systemic antibiotic prophylaxis is recommended by international consensus and represents the standard of care. The recommendations from the major heart rhythm societies clearly indicate to administer antibiotics 1 h prior to skin incision and suggest to prefer drugs that coverage Staphylococcus aureus species such as beta-lactams and glycopeptides. Post-operative antibiotics administration has weak evidence, and its administration varies according to centre and operator practice. Stratification of patient risk at the time of CIED implantation may help to identify those at higher risk of infection. The potential benefit of an extended drug therapy in patients at higher risk needs to be proved. This study was aimed at the evaluation of a new protocol of antibiotic prophylaxis, stratified according to individual infective risk calculated with the Shariff score at the time of CIED implantation.

Methods

The ‘antibiotic PRophylAxis based on infective risk in Cardiac implantable Electronic device—PRACTICE study’ is a prospective, single centre, cohort study.

The study was registered on ClinicalTrials.gov (NCT04736979). The protocol was approved by local ethics committee and informed consent was signed by enrolled patients.

Consecutive patients undergoing CIED surgery in a 3-years period were considered for participation. In particular, patients were eligible if undergoing first implantation or replacement or upgrade of pacemaker or ICD, including CRT, at the Electrophysiology Laboratory of the Cardiological Center of ‘Azienda Ospedaliero-Universitaria S. Anna’, Ferrara (Italy), between 1 January 2017 and 31 December 2019.

Exclusion criteria were: age <18 years, ongoing pregnancy, inability to express informed consent, ongoing antibiotic therapy for reason other than CIED implantation.

At the time of enrolment, before index procedure, the Shariff score was calculated for every patient. In detail, one point was assigned to each of the following factors: diabetes mellitus, heart failure, oral anticoagulation therapy, chronic corticosteroid use, renal insufficiency/failure, prior CIED infection, presence of more than two leads implanted, presence of epicardial leads, use of temporary pacemaker, actual replacement, or upgrade procedure. According to the score, patients were stratified in two groups: low infective risk (score <3) and high infective risk (score >3).

Two different protocols of antibiotic prophylaxis were administered according to risk stratification (Figure 1). Patients in the ‘low-risk’ group were treated with only two doses of antibiotics, both intravenous, of whom the first 1 h before skin incision and the second after 8 hours. Patients in the ‘high-risk’ group were treated with intravenous prophylaxis for two full days (of whom the first administration 1 h before skin incision and the others every 8 h), followed by other 7 days of oral prophylaxis, for a total of 9 days (Figure 1). Thereby, every patient received one administration of intravenous antibiotic 1 h before skin incision and a second administration after 8 h, while patients in the low-risk group did not receive other antibiotics and patients in the high-risk group continued intravenous antibiotics every 8 h for 2 days, followed by oral antibiotics for other 7 days. The intended drug for antibiotic prophylaxis was amoxicillin/clavulanic acid unless the patient had a history of allergic reactions to penicillin. The dosage was dependent on renal function: for intravenous amoxicillin/clavulanic acid 2/0.2 g in patients with creatinine clearance (CrCl) >30mL/min and 1/0.2 g in patients with CrCl <30mL/min, for oral amoxicillin/clavulanic acid 875/125 mg every 8 h in patients with CrCl >30mL/min, and 875/125 mg every 12 h in patients with CrCl <30mL/min. In case of penicillin allergy, clindamycin was chosen. The intravenous dosage of clindamycin was 600 mg every 8 h for CrCl >30 mL/min and 600 mg every 12 h for CrCl <30 mL/min, while the oral dosage was 450 mg every 8 h for CrCl >30 mL/min and 450 mg every 12 h for CrCl <30 mL/min.

Protocol drugs were chosen according to the results of microbiological analysis from biopsy specimen and blood cultures of CIED infections previously reported in our hospital (data previously published).

We followed-up patients for 250 days with clinical outpatient visit and electronic control of the CIED.

As primary endpoint, we evaluated CIED-related infections, considering both those affecting subcutaneous device pocket and those affecting intravascular leads. We also collected data about pocket haematoma, wound complication, lead dislocation, reintervention, pneumothorax, pericardial effusion during index hospitalization. Haematoma was defined as determining prolonged hospitalization (>2 days) or requiring anticoagulant therapy interruption or surgical reintervention. At follow-up, we also collected episodes of heart failure hospitalization and death.

Statistical analysis

Baseline characteristics were summarized as median with inter-quartile interval for continuous variables and frequencies with percentages for categorical variables. The Shapiro–Wilks tests were used to evaluate the continuous variable data distribution. Differences in baseline characteristics according to infective risk were examined using the Wilcoxon rank sum test for continuous variables and the Pearson $\chi^2$ test for categorical variables. Cox proportional hazards regression analysis, with stratification according to the infective risk, was used to calculate the hazard ratio (HR) for each baseline variables. Variables with a $P$-value <0.1 at the univariate analysis were allowed to enter into a stepwise regression model with a backward elimination approach to get the final model. The proportional-hazards assumption was examined with the use of the Schoenfeld residuals. Occurrence of the outcome of interest according to independent predictors was plotted using Kaplan–Meier curves and examined with the use of Log-rank test. All analyses were performed using Stata version 16 (Stata Corp., College Station, TX, USA).
Results
A total of 1044 consecutive patients have been evaluated from 1 January 2017 to 31 December 2019. A total of 80 patients were excluded because of concomitant ongoing antibiotic therapy for reasons other than CIED implantation (i.e. active infection) at the time of procedure, which was considered not deferrable. Other 27 patients were excluded because they did not give informed consent. Thus, study group consisted of 937 patients.

Study population
Baseline characteristics are represented in Table 1. All continuous variables were not normally distributed. Among the enrolled population, 668 patients (71.3%) underwent a ‘de novo’ implantation, while 239 (25.5%) underwent a device replacement, and 30 (3.2%) an upgrade. Procedure details are indicated in Table 2. Median procedure duration was 60 min (inter-quartile interval 50–83).

Median Shariff score was 1 with inter-quartile range 1–2. Shariff score at the time of procedure is represented in Figure 2. According to infective risk stratification, patients considered at low risk (Shariff <3) were 735/937 (78.4%), while patients at high risk (Shariff ≥3) were 202/937 (21.6%). Antibiotic prophylaxis was administered according to study protocol (Figure 1). Fifty-seven patients (6.0%) had a history of allergy to penicillin and were treated with clindamycin.

Outcomes
The primary endpoint, CIED-related infection, occurred in 12/937 patients (1.3%). Of those, eight patients were in the ‘low-risk’ group (8/735, 1.1%) and four in the ‘high-risk’ group (4/202, 2.0%, $\chi^2 = 0.97, P = 0.32$). In three cases the infective event involved the endovascular leads with the development of endocarditis. Details and outcomes of infections are represented in Table 3. Mortality from CIED-related infection was 2/12 (16.7%). Kaplan–Meier curve showing survival free from CIED infection in ‘low-risk’ and ‘high-risk’ group are showed in Figure 3.

Regarding other outcomes, pocket haematoma was more frequent in ‘high-risk’ group compared with ‘low-risk’ group patients (14/202, 6.9% vs. 24/735, 3.3%, $P = 0.019$). No difference between ‘low-risk’ and ‘high-risk’ patients was observed in lead dislodgements (11/735, 1.5% vs. 3/202, 1.5%, $P = 0.99$), reintervention (14/735, 1.9% vs. 7/202, 3.5%, $P = 0.18$), pneumothorax, (7/735, 1.0% vs. 3/202, 1.5%, $P = 0.51$), and pericardial effusion (6/735, 0.8% vs. 3/202, 1.5%, $P = 0.39$).

Finally, hospitalization for heart failure and death during follow-up was more frequent in ‘high-risk’ when compared with ‘low-risk’ group patients (28/202, 13.9% vs. 22/735, 3.0%, $P < 0.001$ and 28/202, 13.9% vs. 62/735, 8.4%, $P = 0.020$, respectively).

Univariate and multivariate analyses
We performed uni- and multivariate analyses to identify factors associated with the primary endpoint (Table 4). At univariate analysis,
active neoplasia, use of P2Y12 inhibitor, haematoma, and reintervention showed a $P < 0.1$ for risk of CIED-related infection. The multivariate analysis showed that only active neoplasia (HR 5.54, 95% confidence interval 1.16–26–54, $P = 0.032$), haematoma (HR 10.77, 95% confidence interval 2.89–40.22, $P < 0.001$), and reintervention (HR 12.15, 95% confidence interval 2.98–49.54, $P < 0.001$) were independently related with CIED-related infection.

Figure 4 shows Kaplan–Meier curves of freedom from CIED-related infection according to CIED pocket haematoma and CIED surgical reintervention, respectively.

**Discussion**

The main finding of this study is that the primary endpoint of CIED-related infection was not significantly different between patients at ‘low risk’ and ‘high risk’ when treated with an antibiotic prophylaxis based on individual stratification of infective risk. Independent predictors of CIED-related infection were active neoplasia, haematoma, and reintervention.

The mechanism leading to the development of infection is mainly due to a bacterial biofilm that can adhere to the device during the implant or in the first days after the procedure, when the cutaneous scar is not completed. Such a biofilm can persist indefinitely, mechanically trapping bacteria in a state in which they are dormant and resist to antimicrobial agents. Various mechanisms are known to contribute to bacterial antimicrobial tolerance and resistance: (i) reduced growth rate; (ii) secretion of different surface molecules and virulence factors; (iii) gene transfer among bacteria which can lead to increase in the number of virulent strains; (iv) extracellular polymeric substances of biofilm matrix retard the diffusion of antibiotics through the biofilm; and (v) bacteria can use multidrug efflux pumps to pump antibiotic agents out of the maturing biofilms and into the extracellular matrix. On this pathophysiological basis, the risk of infection highly depends on the implant procedure; therefore, the antibacterial prophylaxis administered at the time of implantation plays a crucial role in infection prevention for the entire lifetime. The Shariff score has the advantage of immediate easy calculation and allows stratification of patients in high (score $\geq 3$) or low (score $< 3$) risk categories.
Previous studies showed that a Shariff score >3 was an independent predictor of CIED-related infection. Furthermore, the Shariff score has been validated as a predictor of mortality for patients with CIED infections undergoing extraction.

Our study protocol was specifically designed with the aim that patients at high risk would receive a more effective antibiotic prophylaxis with greater appropriateness in an antibiotic stewardship policy. With this approach, patients at low risk treated with short prophylaxis (only two doses) and patients at high risk treated with long prophylaxis (9 days) had similar rate of CIED infection.

In the large, randomized, PADIT Trial, an incremental antibiotic prophylaxis covering the perioperative period and the subsequent 2 days, compared with conventional preprocedural prophylaxis alone, resulted in a modest reduction in CIED-related infection that did not reach statistical significance, probably due to low rates of events. However, the antibiotic protocol was not tailored based on individual infective risk and the prolonged protocol was for only 2 days.

### Table 2 Procedure data

| Variable                        | Study group (n = 937) | Low risk (n = 735) | High risk (n = 202) | P value |
|---------------------------------|----------------------|--------------------|---------------------|---------|
| Implant ‘de novo’               | 668 (71.4%)          | 558 (75.9%)        | 111 (55.0%)         | <0.001  |
| Device replacement              | 239 (25.4%)          | 161 (21.9%)        | 77 (38.1%)          | <0.001  |
| Upgrade                         | 30 (3.2%)            | 16 (2.2%)          | 14 (6.9%)           | <0.001  |
| Pacemaker                       | 754 (80.5%)          | 636 (86.5%)        | 118 (58.4%)         | <0.001  |
| ICD                             | 183 (19.5%)          | 99 (13.5%)         | 84 (41.6%)          | <0.001  |
| Single chamber                  | 420 (44.8%)          | 337 (45.9%)        | 83 (41.1%)          | 0.23    |
| Dual chamber                    | 439 (46.9%)          | 371 (50.5%)        | 68 (33.7%)          | <0.001  |
| CRT                             | 88 (9.4%)            | 29 (3.9%)          | 59 (29.2%)          | <0.001  |
| Presence of temporary pacemaker| 50 (5.3%)            | 27 (3.7%)          | 23 (11.4%)          | <0.001  |
| Number of total leads           |                      |                    |                     |         |
| 1                               | 399 (42.6%)          | 325 (44.2%)        | 74 (36.6%)          |         |
| 2                               | 456 (48.7%)          | 379 (51.6%)        | 77 (38.1%)          |         |
| 3                               | 77 (8.2%)            | 29 (3.9%)          | 48 (23.8%)          |         |
| 4                               | 4 (0.4%)             | 2 (0.3%)           | 2 (1.0%)            |         |
| 5                               | 1 (0.1%)             | 0 (0.0%)           | 1 (0.5%)            |         |
| Procedure duration (min)        | 60 (50–83)           | 60 (50–80)         | 65 (53–90)          | 0.070   |
| Amoxicillin + clavulanic acid   | 880 (93.9%)          | 695 (94.6%)        | 185 (91.6%)         | 0.12    |

Significant P-values are set in bold. CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.
Incidence of infection
In our cohort, 12 patients (1.3%) developed CIED-related infection at 8 months. Literature data from more than 200,000 ICD implantations reported infection rates of 1.7% at 6 months.2 For pacemakers, the large Danish Registry reported an infection rate of 0.48% per year after first implantation and 1.21% after replacement.3 In our Electrophysiology Laboratory, we previously reported an incidence of 1.4%.15 Therefore, our rate of events is consistent with that globally found. This finding leads to the conclusion that CIED-related infections are not frequent but, when they occur, they highly impact...
prognosis. Previous studies reported a mortality rate of 25% at one year.16 Compared with patients with CIED and no infection, infections lead to a 15–20% excess in absolute mortality at one year.17 In our population, mortality from CIED infection was 16.7% at 8 months, consistent with literature.

### Predictors of CIED-related infection

Active neoplasia, haematoma, and reintervention were independent predictors of CIED-related infection. Active neoplasia confirms that fragile patients have higher incidence of complications including infections.18,19 The development of pocket haematoma was strongly associated with CIED infections (HR 10.77, Table 4, Figure 4). Incidence of haematoma in our cohort was 4.1% (38/937 patients), defined as determining prolonged hospitalization or requiring anticoagulant therapy interruption or requiring surgical reintervention. The multicentric Bruise Control-2 study reported an incidence of 2.1% using a similar definition but in a population at lower risk for clinical and procedural characteristics.20 Previously reported incidence in our centre was 1.6% with a more restrictive definition (not including therapy interruption).15 Interestingly, not all infections in patients with haematoma were within the first month but developed during the entire follow-up. A causative relationship is possible, but its demonstration goes outside the purpose of our study. We could only hypothesize that a reduction in the rate of haematoma could reduce the risk of infection. Therefore, a specific management protocol for haematoma prevention is crucial.15

As expected, also CIED surgical reintervention was associated with a high risk of infection (HR 12.15, Table 4, Figure 4) highlighting the deleterious effect of reopening the surgical pocket that is dangerous not only during replacement but also in the early phase after implantation.21–23

### Limitations

This is a single centre, nonrandomized study. However, this study is prospective and based on individual antibiotic prophylaxis depending
on individual infective risk. Patients with ongoing antibiotic therapy for reason other than CIED implantation were excluded. These patients may have a further increase in infection risk but excluding these patients we homogenize our study population and we could better explore the role of individualized antibiotic prophylaxis.

Conclusions

In a large cohort of patients undergoing CIED procedure, an antibiotic prophylaxis based on individual stratification of infective risk resulted in similar rate of infection between groups at high and low risk of CIED-related infections. Active neoplasia, haematoma, and reintervention were confirmed independent predictors of CIED-related infection. These findings may help the management of patients undergoing CIED procedure.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request from the corresponding author.

References

1. Olsen T, Jørgensen OD, Nielsen JC, Thagerson AM, Philbert BT, Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982–2018). Eur Heart J 2019; 40: 1862–9.
2. Prutkin JM, Reynolds MR, Bao H, Curtis JP, Al-Khatib SM, Aggarwal S et al. Rates of and factors associated with infection in 200 909 medicare implantable cardioverter-defibrillator results from the national cardiovascular data registry. Circulation 2014; 130: 1037–43.
3. Johansen JB, Jørgensen OD, Møller M, Arnsbo P, Mortensen PT, Nielsen JC. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J 2011; 32: 991–8.
4. Polyzoa KA, Konstantellas AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. European 2015; 17: 767–77.
5. Sharif N, Eby E, Adelestein E, Jain S, Shalaby A, Saba S et al. Health and economic outcomes associated with use of an antimicrobial envelope as a standard of care for cardiac implantable electronic device implantation. J Cardiovasc Electrophysiol 2015; 26: 783–9.
6. Balla C, Brieda A, Righetto A, Viti A, Malagù M, Cultura R et al. Predictors of infection after “de novo” cardiac electronic device implantation. Eur J Intern Med 2020; 77: 73–8.
7. Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorosed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Europace 2020; 22: 515–49.
8. Nagpal A, Baddour LM, Sohail MR. Microbiology and pathogenesis of cardiovascular implantable electronic device infections. Circ Arrhythm Electrophysiol 2012; 5: 433–41.
9. Bjørkman T. The role of bacterial biofilms in chronic infections. APMS Suppl 2013; 136: 1–5. 10.1111/apm.12099 23633585.
10. Hall-Stoodley L, Stoodley P. Evolving concepts in biofilm infections. Cell Microbiol 2009; 11: 1034–43.
11. Gupta P, Sarkar S, Das B, Bhattacharjee S, Tribedi P. Biofilm, pathogenesis and prevention—a journey to break the wall: a review. Arch Microbiol 2016; 198: 1–15.
12. Hall CW, Mah TF. Molecular mechanisms of biofilm-based antibiotic resistance and tolerance in pathogenic bacteria. FEMS Microbiol Rev 2017; 41: 276–301.
13. Dieminger I, Migliore F, Biffi M, Cipriani A, Bertaglia E, Lorenzo S et al. The “Subtle” connection between development of cardiac implantable electrical device infection and survival after complete system removal: an observational prospective multicenter study. Int J Cardiol 2019; 280: 146–9.
14. Krahn AD, Longtin Y, Philippin F, Birnie DH, Manlucu J, Arangar P et al. Prevention of arrhythmia device infection trial: the PADIT trial. J Am Coll Cardiol 2018; 72: 3098–109.
15. Malagù M, Trevisan F, Scaloni A, Marcantonio L, Sammarco GB, Bertini M. Frequency of “Pocket” hematoma in patients receiving vitamin K antagonist and antiplatelet therapy at the time of pacemaker or cardioverter defibrillator implantation (from the POCKET Study). Am J Cardiol 2017; 119: 1036–40.
16. Greenspon AJ, Eby EL, Petrella AA, Sohail MR. Treatment patterns, costs, and mortality among Medicare beneficiaries with CIED infection. Pacing Clin Electrophysiol 2018; 41: 495–503.
17. Rozvam Sohail M, Henrikson CA, Jo Braid-Forbes M, Forbes KF, Lerner DJ. Increased long-term mortality in patients with cardiovascular implantable electronic device infections. Pacing Clin Electrophysiol 2015; 38: 231–9.
18. Williams MD, Braun LA, Cooper LM, Johnston J, Weiss RV, Qualy RL et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. Crit Care 2004; 8: R291–R298.
19. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carillo J. Pensky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29: 1303–10.
20. Birnie DH, Healey JS, Wells GA, Ayala-Paredes F, Couto B, Sumner GL et al. Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thrombo-embolic events (BRUISE CONTROL-2). Eur Heart J 2018; 39: 3973–9.
21. Poole JE, Gieva MJ, Mela T, Chung MK, Uslan DZ, Borge R, REPLACE Registry Investigators et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. Circulation 2010; 122: 1533–61.
22. Uslan DZ, Gieva MJ, Warren DK, Mela T, Chung MK, Gottipaty V et al. Cardiovascular implantable electronic device replacement and prevention: results from the REPLACE registry. Pacing Clin Electrophysiol 2012; 35: 81–7.
23. Biffi M, Ammendola E, Menardi E, Parisi Q, Narducci ML, De Filippo P et al. Real-life outcome of implantable cardioverter-defibrillator and cardiac resynchronisation defibrillator replacement/upgrade in a contemporary population: observations from the multicentre CODEC registry. Europace 2019; 21: 1527–36.