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ORIGINAL ARTICLE

Outcomes in patients undergoing cardiac resynchronisation therapy complicated by device-related infective endocarditis

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Abstract

Background: Cardiac device-related infective endocarditis (CDRIE) is one of the most serious complications of cardiac resynchronisation therapy (CRT).

Aim: We sought to assess clinical outcomes and their determinants in CRT patients with CDRIE.

Methods: A tertiary cardiology centre database was screened to identify all CDRIE cases, diagnosed based on the modified Duke criteria, amongst 765 consecutive CRT implantations performed between 2002 and 2015 (70.8% de novo implantations, 29.2% upgrades).

Results: During the median follow-up of 1692 days (range: 457–3067 days) CDRIE was diagnosed in 41 (5.4%) patients. Overall, in-hospital and long-term mortality rates of CDRIE patients were 51.2% and 75.6%, respectively. Among patients with CDRIE, in whom the device was vs. was not explanted, in-hospital death rates were 39.3% (11/28 patients) vs. 76.9% (10/13 patients; p = 0.025). In multivariate regression analysis, device removal was independently associated with significantly lower in-hospital mortality (hazard ratio [HR] 0.09, 95% confidence interval [CI] 0.03–0.35, p = 0.0004). The need for temporary pacing after device removal (HR 5.92, 95% CI 1.13–30.96, p = 0.035), a time period of less than seven days between CDRIE diagnosis and CRT removal (HR 6.69, 95% CI 1.48–30.27, p = 0.01), and the highest serum creatinine level during infection (HR 1.02, 95% CI 1.004–1.03, p = 0.01) were identified as independent predictors of higher in-hospital mortality.

Conclusions: Device removal is independently associated with lower mortality in patients with CRT and CDRIE. Early device removal (less than seven days since the diagnosis), the need for temporary pacing after removal and acute renal failure are independent mortality predictors in CRT patients who developed CDRIE.

Key words: cardiac resynchronisation therapy, device-related infective endocarditis, heart failure, mortality predictors

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INTRODUCTION

Cardiac implantable electronic devices (CIEDs) such as pacemakers (PMs), implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) devices are the mainstay of contemporary therapies in cardiology. However, despite growing operators' experience and progressive development in technology, the risks of early and late device-related complications remain considerable [1]. One of the most serious device-related complications is cardiac device-related infective endocarditis (CDRIE), defined as an infection affecting the leads, cardiac valves and/or the endocardial surface [2]. Reported incidence of CDRIE varies from 0.1% to 5.1% and several predisposing factors of CDRIE have been identified so far, such as the lack of antibiotic prophylaxis, use of temporary pacing before the procedure, or implantation of more than two electrodes [3–7]. Mortality rates in CDRIE range from 0%

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to 35% and depend not only on the patients' characteristics but also on the CIED type and its complexity [8–10]. The incidence of CDRIE in CRT recipients seems to be higher than in patients with less advanced CIEDs (e.g. PMs and ICDs), but CDRIE-related mortality rates and predictors thereof in CRT recipients are still unknown.

The aim of this study was to assess clinical outcomes and their determinants in patients with CRT who developed CDRIE.

METHODS

Study population

The study population consisted of all consecutive patients who underwent a de novo CRT implantation or an upgrade from another cardiac device in a high-volume, tertiary care university hospital located in a densely inhabited urban region of Poland, between May 2002 and March 2015. CRT implantation was performed according to the current guidelines of the European Society of Cardiology (ESC). All patients undergoing CRT implantation had to present with symptomatic heart failure (HF) in New York Heart Association (NYHA) class II, III, or IV despite optimal medical treatment, and had to have left ventricular ejection fraction (LVEF) ≤ 35% and wide QRS complexes (in line with the corresponding ESC guideline recommendations). Informed consent for the procedure was signed by all patients. The study complies with the Declaration of Helsinki.

CRT device implantation and removal procedures

The implantation procedure was performed in a standard way in all subjects. Puncture of the subclavian vein or cut-down techniques were used to implant all electrodes endocardially. The position of the left ventricular electrode depended on the venous anatomy as assessed during coronary sinus venography, but the lateral or posterolateral vein was preferred. The choice of the type of leads and the type of device pocket was at the operator's discretion. Intravenous prophylactic dose of antibiotic (cefazoline single dose IV, or clindamycin single dose IV in the case of allergy to cephalosporins) was administered in all patients before the procedure.

Device removal was performed by electrophysiologists in a hybrid cath lab. Routinely, both local (subcutaneous lidocaine) and systemic anaesthesia (e.g. fentanyl IV) were used. Depending on the patient's clinical status either shallow or deep sedation was administered by an anaesthetist. Initially, a traction technique was used to remove the electrodes. If such an approach was not successful, a locking stylet (Liberator, Cook Medical, Bloomington, IN, USA) was routinely employed, particularly in those who had the electrodes implanted more than one year before. In the case of any serious complications cardiac surgeons were immediately available.

Follow-up

Patients were followed up during scheduled visits at one week and one month after the procedure, and subsequently every six months thereafter. Data obtained during unscheduled visits throughout the observation period as well as via hospital records, outpatient notes, telephone calls, and other media from patients, relatives, or death certificates were also analysed. For patients lost to follow-up, data gathered by the insurer (National Health Fund) were used to verify the patient's vital status (and for those who were deceased — to establish the date of death). The follow-up encompassed the whole period from CRT implantation until January 2017 or the subject's death.

Diagnosis and treatment of CDRIE

The study population was screened for CDRIE using the modified Duke criteria [2]. Patients with established CDRIE were treated in line with the ESC guideline recommendations that were in effect at the time of the CDRIE diagnosis. In brief, after the blood cultures had been taken, empirical antibiotic therapy was administered and then changed as appropriate if blood culture tests were positive and susceptibility of pathogens was identified. Alternatively, for negative blood cultures, empirical antibacterial therapy was continued unmodified. CRT removal was considered in all patients with confirmed CDRIE. Due to the lack of any guideline recommendations specifically regarding the optimal timing for device removal, the procedure was performed after antimicrobial pre-treatment, and it was always guided by the patient's clinical condition, e.g. device removal may have been deferred in critically ill patients requiring intensive care.

Statistical analysis

Categorical variables were expressed as numbers and percentages, whereas continuous parameters were expressed as median and interquartile range. The χ^2, Student t test, or Mann-Whitney U test was used as appropriate to compare the groups.

Multivariate Cox regression analyses were performed to identify the independent predictors of all-cause death in CDRIE patients.

A multivariate model was constructed to assess the predictors of all-cause mortality: the first one (model 1) included baseline confounding factors that differentiated the study groups with p-value < 0.05 and the second one (model 2) included the confounding factors with p-value < 0.1.

The results were expressed as hazard ratio (HR) with 95% confidence interval (CI).

A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistica software package (versions 6.0 and 10.0, StatSoft Inc., Tulsa, OK, USA).

RESULTS

Study population

Of 765 patients implanted with CRT between May 2002 and March 2015, CDRIE was diagnosed in 41 (5.4%) subjects until January 2017. The median age in patients with CDRIE was 59 years (range: 48–75 years), ischaemic aetiology of HF was diagnosed in 58.5% of cases, and the median LVEF during the index hospitalisation was 20% (15%–30%) (Table 1). Local device infection was observed in seven (17.1%) patients with CRT-related CDRIE. Positive blood cultures were present in 27 (65.9%) patients. The most common pathogens were *Staphylococci* (n = 16 [59.3%]); *methicillin-sensitive Staphylococcus aureus* (MSSA) was identified in 10 (37%) patients.

Survival and mortality rates in patients with CDRIE

Overall, 31 (75.6%) out of 41 patients who developed CDRIE died during the median follow-up of 1692 days (range: 457–3067 days). Mortality rate during the index hospitalisation was 51.2% (21/41 patients), the remaining 10 subjects died after the median time of 32.3 months (8.5–66.4 months) following the CDRIE diagnosis.

Patients with CDRIE who died, as compared to the survivors, had higher serum baseline creatinine level, were less often treated with gentamycin, more often received inotropes, and less often had their CRT explanted. For those non-survivors who had the device removed, the procedure was performed within seven days from the CDRIE diagnosis and they were more often PM-dependent (requiring temporary pacing after the procedure) (Table 1).

Treatment of infective endocarditis

Of 41 patients with CDRIE, the device was removed in 28 patients and remained in situ in 13 subjects. The corresponding CDRIE-related mortality rates during index hospitalisation were 51.2% (n = 21/41), 39.3% (n = 11/28), and 76.9% (n = 10/13), respectively.

The median time from the CDRIE diagnosis to device removal was 10 days (2–33 days) — a non-different median period amongst those who survived vs. those who died of CDRIE. In two patients, incomplete device removal was performed. One of them died during index hospitalisation, whereas the other was alive at the end of the study period. In comparison to the survivors, patients with CDRIE who died underwent early device removal (i.e. within seven days of the CDRIE diagnosis) significantly more often (Table 1). The median time from CDRIE diagnosis to device removal was three days (range: 2–6 days) in patients explanted within seven days of the diagnosis. In those who were explanted later than seven days from CDRIE diagnosis, the median time to device removal was 16 days (range: 7–42 days). Patients who were explanted < seven days vs. ≥ seven days more often had a coexisting pocket infection (n = 5/11 vs. n = 2/17, p = 0.04) but did not differ with regard to HF severity on admission (NYHA class IV: n = 5/11 vs. n = 12/17, p = 0.18) or use of inotropes during hospital stay (n = 6/11 vs. n = 13/17, p = 0.23). Lead vegetations were observed in 17 (100%) patients in the group of late (≥ seven days) device removal and in seven (63.6%) patients in the group of early (< seven days) device removal (p = 0.007). There were no significant differences between the median size of vegetations between the groups of late and early device removal (12 mm [5–20 mm] vs. 5 mm [5–16 mm]; p = 0.10).

The locking stylet was employed in 18/28 patients, particularly in those who had electrodes implanted earlier than one year before. We observed no differences in survival rates among patients treated with locking stylet vs. those treated without (p = 0.45).

Patients in whom the device was abandoned, compared to patients in whom it was removed, less often had clearly visible vegetations on electrodes (n = 6/13 vs. 24/28, p = 0.008). Of 13 patients with CDRIE who were not explanted, six died before the procedure, three were in critical condition, and one patient was at a very high risk from the procedure itself due to PM dependency and end-stage HF. In the remaining three patients the device was ultimately abandoned (a Heart Team's decision) because of small vegetations and a good response to antibiotic treatment (one patient) and patients' poor condition combined with small vegetations and good response to antibiotics (two cases). A total of 10 out of 13 patients with CDRIE who were not explanted died during hospital stay (in-hospital mortality rate of 76.9%). The median time from CDRIE diagnosis to death was 36 days (range: 4–84 days). Of the remaining three patients who survived the index hospitalisation, two patients died after the median time of 8.5 and 18.7 months, respectively, whereas one patient was alive at the end of the observation (67.6 months from the CDRIE diagnosis).

The device was re-implanted in 18 (64.3%) patients. Of those, the procedure was successful in 15 cases. In two patients re-implantation of a CRT with a defibrillator (CRT-D) failed and ultimately a dual-chamber ICD (ICD-DR) was implanted, and in one patient a single-chamber ICD (ICD-VR) was implanted after a re-assessment of the respective guideline recommendations for device therapy in HF. The median time between device removal and re-implantation was 26 days (range: 16–84 days). After re-implantation, one patient developed endocarditis and died within 29 days. Of 18 patients who were re-implanted, 10 patients died after the median time of 30.7 months (range: 1–52.2 months) and eight were alive at the end of the observation period (median 46.6 months from device re-implantation; range: 18–71.1 months).

Overall, 21 (51.2%) patients were treated with gentamicin. Of those, 14 (70%) patients survived and seven (33.3%) died (p = 0.02). Next to gentamycin, the most common antibiotics were cloxacillin (12 [29.3%] patients;

Table 1. Baseline characteristics of patients with infective endocarditis (CDRIE) in relation to their vital status

	CDRIE			p*
	Overall (n = 41)	Survivors (n = 20)	Deceased (n = 21)	
Age [years]	59 (48–75)	63 (52–75)	58.8 (46–73)	0.29
Male sex	33 (80.5)	15 (75)	18 (85.7)	0.39
NYHA IV at the moment of CDRIE diagnosis	24 (58.5)	9 (45)	15 (71.4)	0.07
Ischaemic aetiology of HF	24 (58.5)	9 (45)	15 (71.4)	0.09
Primary prevention of SCD	29 (70.7)	16 (80)	13 (61.9)	0.20
Arterial hypertension	23 (56.1)	9 (45)	14 (66.7)	0.16
Diabetes mellitus	19 (46.3)	8 (40)	11 (52.4)	0.43
AF/AFL:				
Paroxysmal	12 (29.3)	8 (40)	4 (19.1)	0.14
Permanent	16 (39.0)	5 (25)	11 (52.4)	0.07
LVEF during CDRIE [%]	20 (15–30)	20 (15–38)	19 (15–28)	0.09
Creatinine level at the moment of CDRIE diagnosis [μmol/L]	130 (83–195)	114 (65–157)	136 (105–196)	0.02
NT-proBNP [pg/mL]	7543 (2667–34808)	4523 (835–19936)	11987 (4111–35000)	0.14
hs-CRP [mg/L]	54.6 (5.05–224)	40.8 (1.9–241)	70 (9.9–138.2)	0.95
Upgrade from PM	5 (12.2)	2 (10)	3 (14.3)	0.68
Upgrade from ICD	14 (34.1)	6 (30)	8 (38.1)	0.58
Positive blood culture test	27 (65.9)	11 (55)	6 (28.6)	0.09
Lead vegetations	30 (73.2)	16 (80)	14 (66.6)	0.34
Vegetation size [mm]	10 (5–20)	10 (5–20)	10.5 (5–35)	0.28
Previous AV junction ablation	11 (26.8)	4 (20)	7 (33.3)	0.34
Medication during CDRIE hospitalisation:				
β-blocker	36 (87.8)	19 (95)	17 (80.9)	0.17
ACEI/ARB	28 (68.3)	16 (80)	12 (57.1)	0.12
Aldosterone antagonist	31 (75.6)	17 (85)	14 (66.7)	0.17
Loop diuretic	36 (87.8)	16 (80)	20 (95.2)	0.14
Gentamycin	21 (51.2)	14 (70)	7 (33.3)	0.02
Inotropes	30 (73.2)	11 (55)	19 (90.5)	0.01
Device removal	28 (68.3)	17 (85)	11 (52.4)	0.03
Temporary pacing after removal	11 (39.3)	4 (23.5)	7 (63.6)	0.03
Time from CDRIE diagnosis to CRT removal	10 (2–33)	12 (3–33)	7 (2–26)	0.42
Time from CDRIE diagnosis to CRT removal < 7 days since the diagnosis	11 (39.3)	4 (23.5)	7 (63.6)	0.03
New CRT implantation after removal	18 (64.3)	16 (94.1)	2 (18.2)	< 0.001

Continuous variables are presented as median (interquartile range), categorical variables as numbers (percentages). *p for comparison of CDRIE patients who died vs. survived. ACEI — angiotensin converting enzyme inhibitor; AF — atrial fibrillation; AFL — atrial flutter; ARB — angiotensin receptor blocker; AV — atrioventricular; CDRIE — cardiac device-related infective endocarditis; CRT — cardiac resynchronisation therapy; HF — heart failure; hs-CRP — high sensitivity C-reactive protein; ICD — implantable cardioverter-defibrillator; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro–B-type natriuretic peptide; NYHA — New York Heart Association; PM — pacemaker; SCD — sudden cardiac death

Table 2. Multivariate Cox regression models for the prediction of mortality due to device-related infective endocarditis and all-cause mortality after recovery

Variable	Hazard ratio (95% CI)	p
Predictors of mortality due to CDRIE		
Model 1		
Device removal	0.08 (0.02–0.29)	0.0002
Creatinine level during diagnosis of infection	1.02 (1.004–1.03)	0.009
Time period of less than 7 days between CDRIE diagnosis and CRT removal	6.45 (1.15–36.14)	0.034
The need for temporary pacing after device removal	5.58 (1.03–30.21)	0.046
Inotropes	4.78 (0.73–31.21)	0.102
Gentamycin	0.96 (0.30–3.10)	0.945
Model 2		
Ischaemic aetiology of HF	2.41 (0.65–8.95)	0.189
Positive blood culture	1.51 (0.34–6.60)	0.587
LVEF	0.97 (0.86–1.09)	0.581
Creatinine level during diagnosis of infection	1.02 (1.00–1.03)	0.015
Gentamycin	0.86 (0.23–3.17)	0.822
Inotropes	2.85 (0.19–41.14)	0.442
Device removal	0.03 (0.004–0.17)	0.0001
The need for temporary pacing after device removal	6.29 (0.94–42.16)	0.058
Time period of less than 7 days between CDRIE diagnosis and CRT removal	4.29 (0.74–25.01)	0.105
NYHA IV at the moment of CDRIE diagnosis	0.49 (0.07–3.30)	0.462
Permanent AF	7.69 (1.88–31.59)	0.005
Predictors of all-cause mortality in patients with CDRIE		
Model 1		
Device removal	0.27 (0.12–0.64)	0.003
Creatinine level during diagnosis of infection	1.01 (1.00–1.02)	0.037
Time period of less than 7 days between CDRIE diagnosis and CRT removal	2.74 (0.62–12.08)	0.184
The need for temporary pacing after device removal	2.16 (0.62–12.08)	0.228
Inotropes	3.53 (1.11–11.21)	0.032
Gentamycin	0.72 (0.26–1.99)	0.529
Model 2		
Ischaemic aetiology of HF	1.48 (0.48–4.53)	0.493
Positive blood culture	3.39 (1.38–8.32)	0.008
LVEF	0.97 (0.91–1.04)	0.417
Creatinine level during diagnosis of infection	1.01 (0.99–1.02)	0.079
Gentamycin	0.87 (0.33–2.30)	0.778
Inotropes	2.55 (0.49–13.09)	0.263
Device removal	0.14 (0.05–0.42)	0.0004
The need for temporary pacing after device removal	2.84 (0.88–9.18)	0.081
Time period of less than 7 days between CDRIE diagnosis and CRT removal	6.44 (1.33–31.25)	0.021
NYHA IV at the moment of CDRIE diagnosis	0.72 (0.21–2.46)	0.603
Permanent AF	4.59 (1.65–12.73)	0.003

CI — confidence interval; other abbreviations — see Table 1

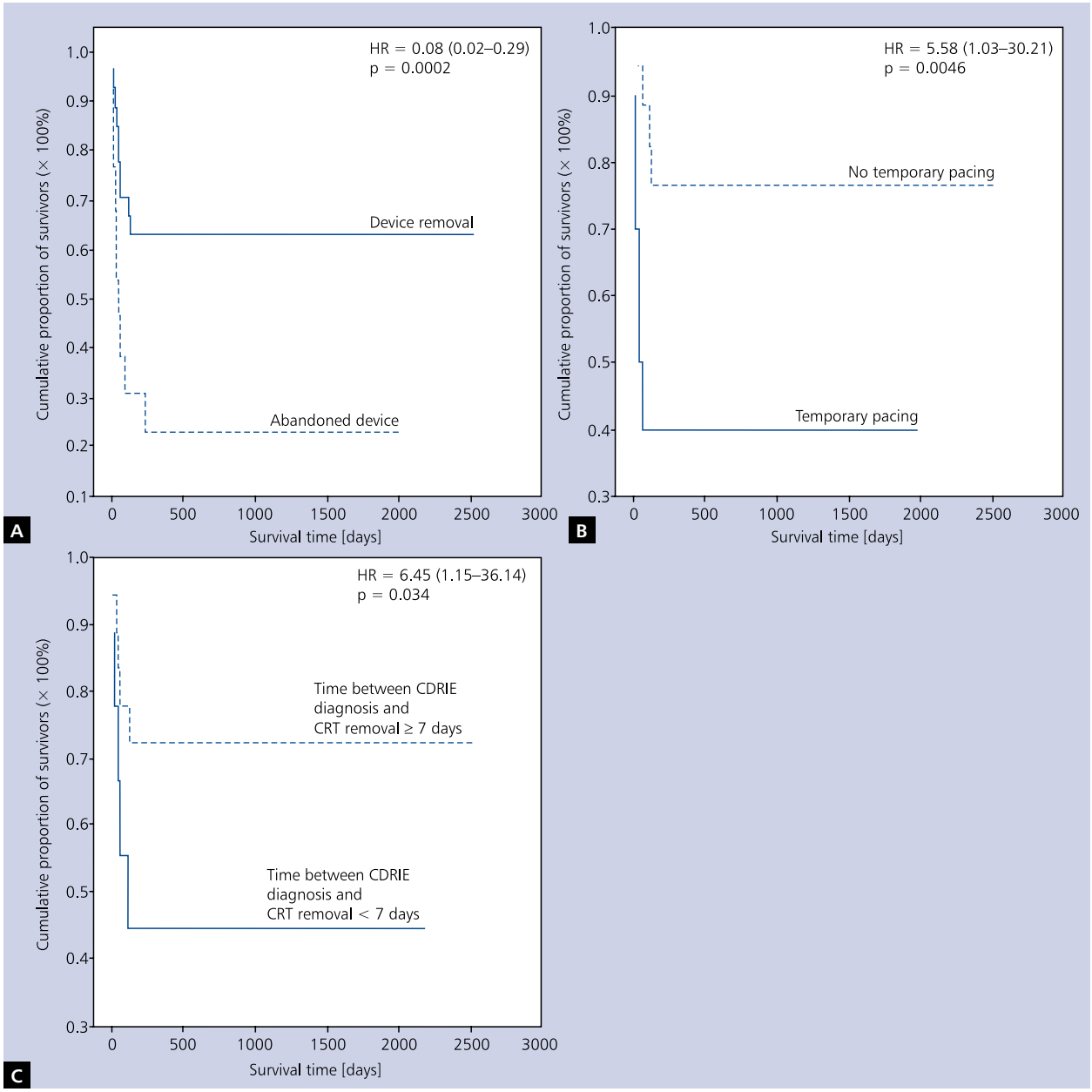

Figure 1. Kaplan-Meier survival curves by independent predictors of mortality: device removal (**A**); the need for temporary pacing after device removal (**B**); and time between the diagnosis of cardiac device-related infective endocarditis (CDRIE) and the removal of cardiac resynchronisation therapy (CRT) device < seven days and ≥ seven days (**C**); HR — hazard ratio

died vs. survived: 5 [12.3%] vs. 7 [17.1%]) and vancomycin (8 [19.5%] patients; died vs. survived: 5 [12.3%] vs. 3 [7.3%]).

Predictors of mortality due to infective endocarditis

The multivariate Cox regression model, including baseline differences as covariates, demonstrated that the need for temporary pacing after device removal (HR 5.58, 95% CI 1.03–30.21, p = 0.046), a period of less than seven days between CDRIE diagnosis and CRT removal (HR 6.45, 95% CI 1.15–36.14, p = 0.03), and higher serum creatinine level during infection (HR 1.02, 95% CI 1.004–1.03, p = 0.009) were independently associated with higher in-hospital mortality rates. Device removal was independently associated with lower mortality rate (HR 0.08, 95% CI 0.02–0.29, p = 0.0002) (Table 2). Kaplan-Meier survival curves by independent factors are presented in Figure 1.

All-cause mortality predictors assessed with the use of the multivariate Cox regression model are presented in Table 2.

DISCUSSION

The main findings of our study are as follows: 1) CRT-related infective endocarditis is associated with a very poor early and long-term prognosis, with more than half of patients dying during index hospitalisation and less than one in four patients surviving the median follow-up of 4.5 years. 2) Abandoned CRT, but also early device removal (< seven days from the CDRIE diagnosis), along with the need for temporary pacing after CRT explantation, and compromised renal function are all independently associated with higher mortality rates. To the best of our knowledge, this is the first study that assessed mortality predictors specifically in patients with CRT-related infective endocarditis.

As reported previously, mortality rates in patients with CRT and CDRIE are very high and may reach 50% during index hospitalisation [11]. In a longer perspective and considering a larger patient population, we report herein in-hospital and long-term mortality rates of 51.2% and 75.6%, respectively. These findings confirm worse outcomes of CDRIE in CRT recipients in comparison with patients implanted with less advanced devices, such as ICDs or PMs, in whom the mortality rates vary from 13% to 33% [8–10, 12]. There may be various potential reasons for better outcomes in the latter group, e.g. evident differences in clinical characteristics, no signs of or less advanced HF, less frequent PM dependency, etc. [10, 12].

The ESC guidelines recommend complete device removal in all cases of confirmed CDRIE, because antibiotic therapy alone is associated with poor outcomes [13–15]. Consequently, European experts do not recommend the consideration of important device- and patient-related factors such as device type (PM, ICD, CRT), PM dependency, infection duration/control, or the patient's clinical status (e.g. critical vs. stable) in decision making regarding CDRIE treatment. In addition, optimal timing for device removal has never been assessed, and thus no specific recommendations have been issued.

There are no studies that prospectively compare various treatment strategies on clinical outcomes in CDRIE, i.e. antimicrobial treatment alone vs. combination therapy (antibiotic treatment with device removal). A few reports showed higher mortality rates in patients with CDRIE treated with antimicrobial agents alone vs. those treated with combination therapy, with corresponding mortality rates reaching 31% to 66% vs. 13% to 33%, respectively [15, 16]. Nonetheless, these studies were based on small groups of patients (e.g. smaller than in the present analysis) and included only patients with PMs or ICDs. In contrast, data on CDRIE in CRT recipients are scarce. The optimal treatment strategy for CRT-related CDRIE has never been established, and thus a simple repetition of therapy regimens suggested for PM/ICD patients may not be the most appropriate approach.

As in PM/ICD patients, herein we report that survival rates for CRT recipients with CDRIE are significantly better if the system is explanted. This finding may not be surprising because removal of a device covered by bacterial vegetations is supposed to eliminate the source of systemic infection. Moreover, device removal seems to be reasonable also in patients with a very high probability of CDRIE (as suggested by the patient's clinical status, positive blood cultures, and treatment effects) but with no clear vegetations on transoesophageal echocardiography. This assumption may be confirmed by our findings. Indeed, we observed very high mortality rates in both critically ill patients and in those with no clearly visible vegetations, unless the device was removed.

Importantly, we show herein that timing of device removal in CRT recipients may also be an important factor. We found that early CRT removal (less than seven days from CDRIE diagnosis) was independently associated with higher hospital mortality than in patients in whom the device removal was deferred. We may only speculate on potential reasons for more beneficial effects of deferred vs. early device removal. First, CRT patients may benefit from longer (more than seven days) antibiotic pre-treatment. Such an approach may help control bacteraemia and improve the patient's clinical status. Second, in contrast to PM/ICD devices, removal of the CRT is always associated with abrupt loss of biventricular pacing. Importantly, maintenance of a high percentage of biventricular pacing is the mainstay of effective HF treatment in CRT recipients, and even very short periods (< seven days) of biventricular pacing loss have been reported to increase mortality [17]. It seems that maintenance of biventricular pacing in acutely ill patients with bacteraemia, particularly in those with septic shock, may even be more important than early elimination of the infection source. Nonetheless, once the infection is better controlled and the patient's condition is stable, device removal seems inevitable. The net clinical benefit, when balancing the need for early infection control (device removal) vs. maintenance of haemodynamic stability and HF control, needs to be established in a well-designed randomised clinical trial.

Lack of biventricular pacing may be even more important for PM-dependent patients. Indeed, our data show that the need for temporary pacing after device removal was independently associated with substantially higher mortality. The abrupt replacement of resynchronisation with the stimulation of only the right ventricle may further worsen the haemodynamic status of these severely ill patients [18, 19]. Also, temporary pacing itself has been previously shown to be a risk factor for CDRIE development, which may additionally hamper effective infection control [12].

Higher creatinine level was also a predictor of poor outcome in our study. Many previously published studies have highlighted the importance of renal dysfunction in different patient groups including subjects with endocarditis [20]. The association between renal function and mortality seems to be especially strong in patients with HF [21]. There are many po-

tential mechanisms behind this association. Higher creatinine concentration may be a marker of more severe HF. Patients with renal impairment may not be the best candidates for optimal (aggressive, often causing renal function impairment) pharmacotherapy. They are more likely to receive suboptimal doses of angiotensin converting enzyme inhibitors and/or aldosterone antagonists, and the choice of antimicrobial treatment is also affected by renal function.

A major limitation is of this study is the small sample size. Nonetheless, previous reports on the topic were also hampered by small, or at best moderate, populations of patients with CDRIE. This is a retrospective, single-centre observation, which may limit patient representativeness and thus the generalisability of findings. However, our data come from a high-volume, tertiary university centre covering a densely populated region of over four million inhabitants, which reflects real-life implantation rates and CDRIE incidence in this region of Poland. In addition, we analysed every case of CRT-related CDRIE from May 2002 through January 2017. However, we did not perform additional tests such as positron emission tomography (PET) or single photon emission computed tomography-computed tomography (SPECT-CT) in our patients with suspected CDRIE, thus we cannot exclude that some subjects with CDRIE were overlooked. The use of additional tests such as PET or SPECT-CT was proposed in the ESC guidelines, but validation of these methods in CDRIE is still needed [22]. Finally, our regression analyses may be affected by insufficient events per covariate. Nonetheless, previously published studies with low incidence of events used a similar approach for multivariate regression analyses.

Our data are hypothesis-generating only and should not suggest that deferred versus early device removal is superior in patients with CDRIE. Only a well-designed and adequately powered randomised clinical trial comparing different treatment strategies (i.e. early vs. postponed device removal) could provide a conclusive answer to those pending clinical questions.

In conclusion, more than half of CRT patients with CDRIE do not survive index hospitalisation. Device removal is independently associated with lower mortality in patients with CRT and CDRIE. Early device removal (less than seven days since the diagnosis), the need for temporary pacing after the removal, and acute renal failure are independent mortality predictors in patients with CRT, who develop CDRIE.

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WHAT IS NEW?

Cardiac device-related infective endocarditis (CDRIE) that develops in cardiac resynchronisation therapy (CRT) recipients is associated with a very poor early and long-term prognosis, with more than half of patients dying during index hospitalisation and less than one in four patients surviving the median follow-up of 4.5 years. Device removal is independently associated with lower mortality in CRT patients with CDRIE. Among patients with CDRIE in whom the device was explanted, in-hospital death rates was 39.3%, whereas among patients in whom the device was abandoned it reached 76.9%. Although CRT explantation is independently associated with survival benefit, early device removal (less than seven days from CDRIE diagnosis), the need for temporary pacing after CRT removal, and compromised renal function are all independently associated with higher in-hospital mortality in CRT patients who developed CDRIE.