CHAPTER XII

Cardiac Device Infections are Associated With a Significant Mortality Risk

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ABSTRACT

Background: Cardiac device infections (CDIs) are a serious complication associated with the implantation of cardiac rhythm devices. However, the effect of CDI on the subsequent risk of mortality is unknown.
Objective To assess the prognostic importance of CDI in recipients of implantable cardioverter-defibrillator and cardiac resynchronization therapy – defibrillator.

Methods: All patients who received their initial implantable cardioverter-defibrillator/cardiac resynchronization therapy – defibrillator between January 2000 and September 2009 were included. During follow-up, the occurrence of CDI and all-cause mortality were noted. The prognostic importance of the first CDI on mortality was assessed by modeling CDI as a time-dependent covariate in the Cox proportional hazards model.

Results: A total of 2476 patients (79% men; mean age 62 ± 13 years) were included in this analysis. During follow-up, CDI occurred in 64 (2.6%) patients. The 1-year mortality following first CDI was 16.9% (95% confidence interval 6.7%–27.1%). Experiencing the first CDI was associated with a 1.9-fold (hazard ratio 1.87; 95% confidence interval 1.07–3.26) increased risk of mortality compared to patients who did not experience CDI. After controlling for possible confounders, this increased to a 2.4-fold (hazard ratio 2.40; 95% confidence interval 1.35–4.28) increased risk of mortality.

Conclusions: In a large cohort of patients who receive implantable cardioverter-defibrillator/cardiac resynchronization therapy – defibrillator after their initial implant, the 3-year incidence of CDI was 2.6%. The occurrence of CDI was associated with substantial 1-year mortality, and patients experiencing CDI had a more than 2-fold increased risk of mortality compared with patients who remained free from CDI.

INTRODUCTION

In the past decades, evidence-based indications for the implantation of cardiac rhythm devices expanded rapidly, resulting in a large increase in the number of device implantations.[1-6] The incidence of complications, of which cardiac device infections (CDIs) are among the most important, also increased subsequently, and it has been reported that the increase in the incidence of CDI has outpaced the increase in implantation rates.[7-9] Current annual CDI rates vary from ~1% after the first device implant up to 7% after device replacements and/or upgrades.[10-12]

CDIs present with a broad range of symptoms, varying from local complaints at the generator pocket site to severe systemic manifestations, and are associated with substantial morbidity and mortality.[13] In addition to this high morbidity and mortality, CDI is associated with significant costs, which have been estimated at $50,000 per patient.[14]

Despite several studies reporting on considerable mortality rates following CDI, no risk assessments were conducted. The extent to which patients with CDI are at increased risk of death as compared with those who remain free from this condition is therefore yet unknown. The objective of this study was to assess the incidence, pathogens, and prognostic importance of CDI in recipients of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy – defibrillator (CRT-D).

METHODS

Patient selection

At our tertiary care facility (Leiden University Medical Center, Leiden, The Netherlands), data of all patients who receive an ICD or CRT-D are recorded in the departmental cardiology information system (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands). At baseline, information of the implant procedure and clinical characteristics is collected and all ICD/CRT-Ds are interrogated during regular follow-up. For the current study, all patients who received their initial ICD or CRT-D system between January 2000 and September 2009 were included.

Device implantation

All ICDs and CRT-Ds were implanted in the pectoral region, and pacing, sensing, and defibrillation thresholds were tested during implantation. Used device systems were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN), Boston Scientific (Natick, MA), and St Jude Medical (St Paul, MN). Flucloxacillin or, in the case of a prior allergic reaction, vancomycin was administered immediately prior to the ICD implantation, and in the case of flucloxacillin also 4 hours after the procedure. In the case of generator replacement without lead replacement, antibiotics were administered only prior to the procedure.

Patient follow-up

Patients were followed up every 3–6 months or earlier in the case of symptomatic events. Moreover, at 2 months and 1 year following implantation, the cardiac device pocket was examined externally. Patients with missing data for more than 6 months were considered lost to follow-up. For the current analysis, patients were followed up from the initial ICD/CRT-D implant date until the last device follow-up date before September 2009.

CDI

Patients presenting with endocarditis, with or without signs of vegetation on the leads, and patients with infective symptoms at the generator pocket site were referred for device extraction because of suspected CDI. Patients presenting with persistent fever or recurrent bacteremia without an apparent focus, despite profound examination, were also referred for device extraction since a CDI could not be excluded. CDI was microbiologically confirmed on the basis of positive cultures from the generator pocket, leads, and/or blood samples. In patients in whom multiple infections occurred, only the first event was used in the analyses.

Statistical analysis

When normally distributed (as assessed by the Kolmogorv–Smirnov test), continuous variables are expressed as mean ± SD, and when non-normally distributed, as median (25th and 75th percentiles Q1, Q3). Continuous data were compared by using the Student t test for unpaired data. The χ^2 test was used to compare categorical variables. Cumulative incidences for all-cause mortality and the occurrence of CDI were estimated by using Kaplan–Meier curves. To assess whether the occurrence of CDI was associated with an increased mortality, Cox proportional hazards modeling was used with CDI modeled as a time-dependent covariate. In addition, potential confounders (age, sex, renal function, and diabetes mellitus) were included in the multivariate analysis. Predictors of mortality after CDI were determined by using Cox proportional hazards modeling. Initially, univariate analysis was performed among baseline variables. Subsequently, all variables with a P value of <.25 were included in the multivariate model. A P-value of <.05 was considered statistically significant. All statistical analyses were performed by using PASW Statistics, version 18.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient population

Between January 2000 and September 2009, 2574 patients received their initial ICD or CRT-D. Of these, 98 (3.8%) patients were considered lost to follow-up. The remaining 2476 patients (79% men; mean age 62 ± 13 years) were included in this analysis. The majority of these patients received an ICD (59%) and had ischemic heart disease (64%). Table 1 summarizes their baseline characteristics.

Table 1: *Baseline characteristics*

Clinical Parameters	
Age (yrs)	62 ± 13
Male, nr. (%)	1948 (79%)
Primary prevention, nr. (%)	1631 (66%)
Ischemic heart disease, nr. (%)	1579 (64%)
Left ventricular ejection fraction (%)	33 ± 15 %
Renal clearance (mL/min/1.73m^2)	81 ± 36 mL/min/1.73m^2
QRS duration (ms)	125 ± 35
NYHA class III or IV, nr. (%)	831 (34%)
History of smoking, nr. (%)	1163 (47%)
Diabetes, nr. (%)	532 (22%)
Devices	
ICD, nr. (%)	1465 (59%)
CRT-D, nr. (%)	1011 (41%)

CRT-D = cardiac resynchronization therapy – defibrillator; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association

CDI

During a median follow-up of 30 [14, 55] months, 64 of the 2476 patients (2.6%) underwent device and lead extraction for CDI. Local complaints (swelling, pain, warmth, and skin discoloration) at the generator site were the most common symptom in patients with CDI (88%). However, systemic signs of CDI were also often present: ~40% presented with fever and/or positive blood cultures. Table 2 summarizes the patient characteristics and clinical presentation of the patients experiencing CDI.

The median time between the last pocket-related procedure (eg, implantation, lead revision, or generator exchange) and explantation because of CDI was 6 [1, 17] months. The cumulative incidence of CDI was 1.1% (95% confidence interval [CI] 0.7%–1.5%) at 1-year follow-up. Hereafter, this incidence steadily increased to 2.6% (95% CI 1.8%–3.4%) at 3-year follow-up. As can be seen in Figure 1, at 4.5 years the cumulative incidence of CDI increased exponentially: yearly incidence in the first 3 years was 0.9% vs 1.7% between 4.5 and 6 years of follow-up.

All but one (92%) patient, in whom CDI occurred >4.5 years after the initial device implantation, had undergone a generator exchange before the occurrence of CDI (median duration between generator exchange and CDI 5 [1, 18] months).

Microbiology

The most common pathogens cultured from the infected site were Staphylococcus aureus (25%) and coagulase-negative Staphylococcus (20%). The distribution of the pathogens is

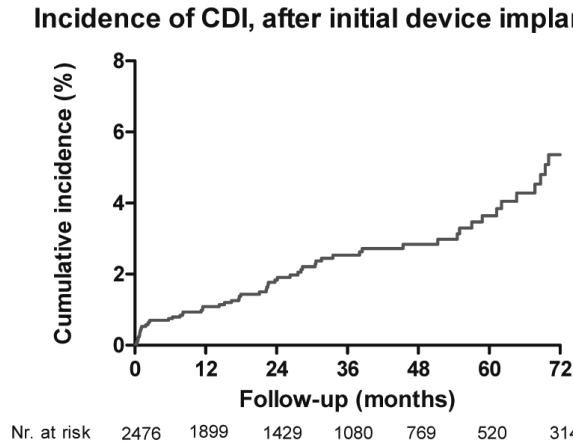

Figure 1. Kaplan-Meier curve for the cumulative incidence of cardiac device infections after the initial device implantation

Table 2: *Characteristics and clinical presentation of patients with CDI (n=64)*

Characteristics	
Age (yrs)	60 ± 15
Male gender, nr. (%)	54 (84%)
Diabetes Mellitus, nr. (%)	12 (19%)
Left Ventricular Ejection Fraction (%)	36% ± 15
Renal clearance < 60mL/min/1.73m^2, nr. (%)	16 (25%)
Presenting sings/symptoms	
Early infection*	25 (39%)
Local complaints**, nr. (%)	56 (88%)
Impending lead / generator erosion, nr. (%)	15 (23%)
Lead / generator erosion, nr. (%)	8 (13%)
Fever, nr. (%)	23 (36%)
Systemic signs of infection, nr. (%)	26 (41%)
Leukocytosis (WBC > 10 x 10^9 / L, n = 60), nr. (%)	16 (27%)
Elevated CRP (CRP > 10 mg/L, n = 51), nr. (%)	33 (65%)
Positive blood culture (n = 43), nr. (%)	15 (35%)

*Infection becoming apparent <60 days after last pocket related procedure; **Local complaints included: swelling, skin discoloration, pain, warmth; CRP = C-reactive protein; WBC = white blood cell count

summarized in Table 3. This table also shows the number of positive cultures vs the total number of available cultures stratified per culture type and causative pathogen. There was

Table 3: *Distribution of pathogens and frequency of positive cultures stratified per culture type (n=64)*

Identified pathogen n(%)		Blood	Tissue	Swab	Leads
		+ / total (%)	+ / total (%)	+ / total (%)	+ / total (%)
S. Aureus	16 (25%)	9 / 14 (64%)	6 / 6 (100%)	14 / 14 (100%)	12 / 13 (92%)
CNS	13 (20%)	1 / 6 (17%)	7 / 9 (78%)	12 / 12 (100%)	11 / 11 (100%)
P. acnes	6 (9%)	0 / 6 (0%)	3 / 3 (100%)	5 / 6 (83%)	6 / 6 (100%)
Polymicrobial	9 (14%)	1 / 7 (14%)	7 / 7 (100%)	9 / 9 (100%)	8 / 8 (100%)
Other	14 (22%)	4 / 6 (67%)	2 / 3 (67%)	10 / 11 (91%)	12 / 12 (100%)
Negative	5 (8%)	0 / 4 (0%)	0 / 2 (0%)	0 / 4 (0%)	0 / 3 (0%)
No cultures	1 (2%)				
Total	64 (100%)	15 / 43 (35%)	25 / 30 (83%)	50 / 56 (89%)	49 /53 (92%)

For each identified pathogen the number of positive (+) cultures vs. the total number of available cultures are shown stratified per culture type. For instance *S. Aureus was the causative agent in 16 (25%) patients. In 14 out of 16 patients blood cultures were taken, which were positive in 9. Therefore 64% (9 out of 14) of the blood cultures were positive in patients with S. Aureus as the causative agent.* S. Aureus = staphylococcus aureus; CNS = coagulase negative staphylococcus; P. acnes = propionibacterium acnes.

a significant difference in the fraction of positive cultures between different culture types: lead cultures were positive in 92%, whereas blood cultures were positive in only 35% of the available cultures (P <.01).

There was a significant relationship between the type of microorganism cultured and the presence of systemic signs of infection: S. aureus was most often cultured in patients with systemic signs of infection (42%; P <.05). S. aureus also appeared to be most commonly associated with early infections (44% of early infections caused by S. aureus). However, this was not statistically significant (P = .09).

Complications of device explantation

No patient presenting with their first CDI died during hospitalization, and no major complications associated with the device explantation occurred; in other words, all leads and devices could be removed safely. A relapse of CDI was observed in 3 of the 64 patients (4.7%). One patient presenting with a relapse of CDI died directly after the second explantation procedure owing to a septic shock. The median duration between device explantation and new device implantation was 16 [11, 22] days.

Effect of CDI on survival

During the follow-up period, 407 (16.4%) patients died. The 1-year and 3-year cumulative mortality rates were 5.6% (95% CI 4.6%–6.6%) and 14.0% (95% CI 12.4%–15.6%), respectively (Figure 2). The absolute mortality was 5.4 per 100 patient-years.

In patients presenting with CDI, 1-year and 3-year cumulative mortality rates after device explantation were 16.9% (95% CI 6.7%–27.1%) and 27.5% (95% CI 14.4%–40.6%),

respectively (Figure 3). The absolute mortality was 10.2 per 100 patient-years.
Cox proportional hazards regression analysis demonstrated that for patients presenting with CDI, the risk of death was 1.9 times higher than that for patients who remained free of CDI

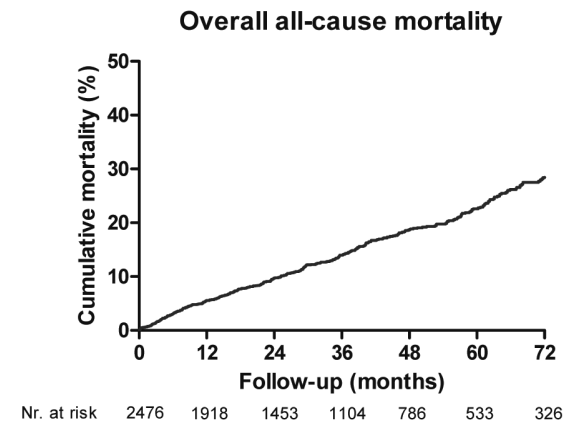

Figure 2. Kaplan Meier Curves showing the cumulative mortality after initial device implantation.

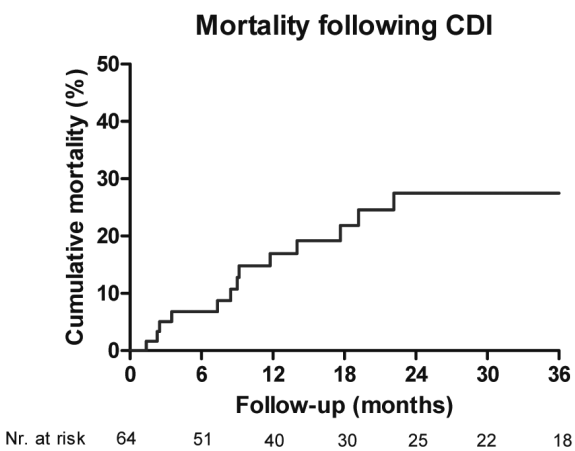

Figure 3. Kaplan Meier Curves showing the cumulative mortality after cardiac device infection.

(hazard ratio 1.87; 95% CI 1.07–3.26; P = .027). After adjustment for potential confounders (age, gender, renal clearance, and diabetes mellitus), the relative risk of all-cause mortality, associated with CDI, increased to 2.40 (95% CI 1.35–4.28; P = .003).

Factors associated with mortality after CDI

In order to establish clinical parameters associated with mortality after CDI, uni- and multivariate subanalyses were performed. Multivariate analysis, including parameters with a P value of <.25 in the univariate analysis, revealed that female gender and an impaired

Table 4: *Predictors of mortality after CDI*

Parameter	Univariate	P	Multivariate	P
Age	1.01 (0.97 -1.05)	0.63		
Female Gender	4.48 (1.50 – 13.43)	0.007	4.02 (1.30 – 12.37)	0.015
Diabetes Mellitus	1.17 (0.26 – 5.31)	0.84		
eGFR ≤ 60ml/m2	4.90 (1.62 -14.80)	0.005	4.50 (1.44 – 14.00)	0.009
LVEF, (%)	0.98 (0.94 – 1.02)	0.34		
Early infection	1.22 (0.41 – 3.64)	0.72		
S. Aureus Infection*	1.39 (0.14 – 13.56)	0.78		
Systemic Infection**	1.52 (0.51 – 4.51)	0.46		

All parameters with a p<0.25 in the univariate analysis were included in the multivariate analysis.
*Compared to negative cultures; ** Fever and/or positive blood cultures.

renal function, defined as an estimated glomerular filtration rate ≤ 60 mL/min/1.73 m2, were independent predictors of mortality after CDI (hazard ratio 4.02; 95% CI 1.30–12.37 and hazard ratio 4.50; 95% CI 1.45–14.00, respectively). Table 4 shows the results of the univariate and multivariate analyses.

DISCUSSION

In our study, the cumulative incidence of CDI in a large cohort of recipients of ICD and CRT-D was 1.1% at 1 year and 2.6% at 3 years after the initial device implantation. Ninety-two percent of late-occurring CDIs (>4.5 years after the initial device implantation) were observed following generator replacement. Importantly, those with CDI had 1-year and 3-year cumulative mortality rates of 16.9% and 27.5%, respectively, following device explantation, reflecting a 2-fold increased risk of death in patients experiencing CDI compared with those who remain free from this condition. Female gender and impaired renal function were independent predictors of mortality following CDI.

Incidence of CDI

In this study, the cumulative incidence of CDI is in line with previously published literature.[10,15]

Of particular interest is the increase in the infection rate ~4.5 years after the initial device implantation. The probable explanation could be the fact that around this time, generator batteries become depleted and require exchange.[16,17] Generator exchange is a well-established risk factor for developing CDI and other pocket-related complications.[10,11,18]

Increased risk of mortality

Previously reported mortality associated with CDI is comparable to the findings of this study.[19] However, the difference in mortality in patients with CDI compared with patients

who remain free from CDI, in other words the prognostic importance of CDI, has not previously been established. In the current population, the difference in mortality rates between patients experiencing CDI and those who remained free from this condition was also established by using CDI as a time-dependent covariate. CDI was associated with a 2.4-fold increased risk of mortality for patients who experienced CDI compared with patients who remained free from this condition, underscoring the prognostic importance of this condition. One might postulate several reasons for the higher mortality in patients who experience CDI, including (1) mortality might be directly related to CDI (ie, septic shock), (2) mortality might be associated with the treatment of CDI (ie, device and lead explantation, new device implantation, and the hospitalization itself), and (3) patients experiencing CDI may have a higher incidence of comorbidities, such as renal failure, which are associated with a higher chance of developing CDI and also with an increased mortality.

Prevention strategies

With regard to the prevention of CDI, several preoperative measurements should be taken. Before implantation, it is important to ensure that the patient does not have clinical signs of infection. Furthermore, prophylactic antibiotics should be administered before the device implantation.[20] In addition, postoperative complications needing reintervention, such as the development of hematomas at the generator pocket site, are strongly associated with the development of CDI. Prevention of the development of pocket hematomas is therefore warranted and periprocedural antiplatelet/anticoagulation regimens might need to be adjusted, depending on possible risks and benefits.[21, 22, 23]

Despite the mentioned prevention strategies, the incidence of CDI increases and novel treatment strategies are therefore being investigated. These prevention strategies might become useful in the near future and might have beneficial effects, especially in high-risk patients. For instance, it has been recently demonstrated that an antimicrobial pouch reduces the incidence of CDI in an in vivo model.[24] Also, a totally subcutaneous ICD and a leadless pacing system might serve as potential strategies to reduce the incidence of infection.[20]

Furthermore, in light of the increased risk of CDI after patients had undergone generator replacement, improving the longevity of cardiac rhythm devices should be considered an important prevention strategy.

CONCLUSIONS

CDI is a condition that might have serious implications. The incidence of CDI is 2.6% 3 years after the initial device implantation. Furthermore, the annual incidence appears to increase from 4.5 years after the initial device implantation. CDI is associated with a 2.4-fold increased risk of mortality compared to patients in whom CDI does not occur, necessitating the development of effective preventive strategies.

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