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Chapter 3

Recurrent Implantable Cardioverter-Defibrillator Replacement is Associated with an Increasing Risk of Pocket-related Complications



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ABSTRACT

Background

Despite the positive effect on mortality of ICD therapy in selected patients, limited service life of the ICD results in a necessity of replacement in the majority of patients. Data on the effect of replacement procedures on the occurrence of pocket related adverse events are scarce.

Methods and Results

Since 1992, a total of 3161 ICDs were implanted in 2415 consecutive patients (80% men, mean age 62 (SD 13) years) ICDs were grouped by the consecutive number in which they were implanted, resulting into a group of first implanted ICDs and multiple groups of consecutive replacement ICDs. All pocket related complications requiring surgical re-intervention following ICD implantation or replacement were noted. In total, 145 surgical re-interventions were required in 122 (3.9%) patients, with a median time to first re-intervention of 75 days. The three years cumulative incidence of first re-intervention was 4.7% (95% CI 3.9-5.5%) and the incidence of re-intervention was 1.9 (95% CI 1.6-2.2) per 100 ICD-years. Event rate comparison of replacement ICDs versus first implanted ICDs showed a more than doubled need for re-interventions in replacement ICDs (rate ratio 2.2 [95% CI 1.5-3.0]). Further subdivision by the consecutive number of ICD replacements, shows an increase in the annual need for surgical re-intervention, ranging from 1.5% (95% CI 1.2-1.9%) in the first implanted ICD, to 8.1% (95% CI 1.7-18.3%) in the fourth implanted ICD.

Conclusion

ICD replacement is associated with a doubled risk for pocket related surgical re-interventions. Furthermore, the occurrence of the need for re-intervention increases with every consecutive replacement.



INTRODUCTION

Implantable cardioverter-defibrillators (ICDs) have shown to be an effective treatment modality in the primary and secondary prevention of sudden cardiac death in selected patients.¹⁻⁷ With expanding indications for ICD therapy, worldwide implantation rates have increased to an estimated 275,000 units in 2008.^{8,9} Although these major advances have a positive effect on mortality, some serious drawbacks of ICD therapy should not be overseen. The most important being the limited service life of the pulse generator, resulting in device replacement approximately every 4-5 years.^{10,11} With increased survival of patients it is estimated that over 70% of implanted patients require an ICD replacement due to end-of-life of the device and 40% even require a second replacement.¹¹ These figures imply that the number of can be expected to outnumber first implantations in the near future.¹² Previous studies have demonstrated that surgical re-interventions, such as device replacements, are correlated to an increased occurrence of device infections.^{13,14} Additionally, Gould and Krahn reported that the consequences of an early re-intervention for a non-infectious cause can be considered more harmful than the underlying complication itself.¹⁵ However, the effect of replacement on non-infectious, pocket related complications and the effect of additional replacements has not yet been assessed.

This current increase in ICD replacements warrants clear mapping of the associated risks for complications, such as hematoma or infection. In this analysis a comparison is made to determine the requirement for pocket related surgical re-intervention in first implanted ICDs and replacement ICDs in a large number of implanted ICDs (n= 3161).

METHODS

Patients

The study population consisted of consecutive patients who received an ICD system in the Leiden University Medical Center. Since 1992 all implant procedures were registered in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Data of the implant procedure and all follow-up visits were recorded prospectively. The data collected for the current registry ranged up to August 2008. Abdominal implanted ICDs were excluded from the current analysis.

Indications for ICD treatment were made according to international guidelines at that time. Due to evolution of these guidelines, indications will have changed over time.^{8,16} Majority of patients were indicated for ICD treatment in the presence of prior life-threatening ventricular arrhythmia or poor left ventricular ejection fraction [LVEF].

Device implantation and discharge

At implantation, patients were clinically assessed, as described previously.¹⁷⁻¹⁹ During the implant procedure testing of sensing and pacing thresholds and defibrillation threshold testing was performed. Before discharge all patients underwent pocket inspection to exclude hematoma or early signs of infection. If no abnormalities were found and temperature was normal, patients were discharged.

End-point and follow-up

The primary end-point was the occurrence of a surgical re-intervention of the ICD pocket (not because of an elective device replacement, lead failure or device malfunction). Since the aim of the current study was to evaluate the differences in event-rates between first implanted ICDs and replacement ICDs, only pocket related causes were considered. If other causes, such as lead related complications or pulse generator malfunction were taken in account, comparison would be difficult, given the fact that commonly, leads are only implanted at the initial ICD implantation and can therefore not be compared to lead related complications at replacement.

In the Dutch health care system, all patients are followed by the implanting center and periodical follow-up was performed every three to six months. This study included follow-ups performed up to September 2008. During periodical follow-up the pocket was inspected for abnormalities and ICDs were checked at their functionality and battery status.

Since periodical follow-up was performed every three to six months, patients with more than six months of missing data were considered as lost to follow-up.

Statistical analysis

Continuous data are expressed as mean and standard deviation or range, median and first and third quartile where appropriate; nominal data are presented as numbers and percentages. ICDs were grouped by the consecutive number in which they were implanted in the patient. This classification divides the implanted ICDs into a group of first implanted ICDs and multiple groups of replacement ICDs. The number of required re-interventions and the sum of years the ICDs were followed-up (ICD-years) were calculated for each group. Event rates were calculated by dividing the number of surgical re-interventions by the number of ICD-years, expressed with a two-sided 95% confidence interval (95% CI). In the calculation of the 95% CI for event rates, a Poisson distribution of the observed number of events was presumed. Rate ratios were used to assess the differences in event rates between groups. Cumulative incidences were analyzed with the method of Kaplan-Meier. For all tests, a p-value <0.05 was considered significant.

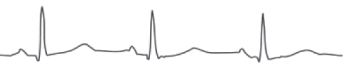
RESULTS

Defibrillator implantations

A total of 3328 ICDs were implanted in 2521 patients between 1992 and August 2008. For the current analysis, all abdominal (n= 102, 3%) placed ICDs were excluded. Sixty-five (2.0%) ICDs were lost to follow-up. The remaining 3161 devices, implanted in 2415 patients were included in the analysis. These consisted of 2415 (76%) first implanted and 746 (24%) replacement ICDs. Figure 1 shows the annual proportion of replacements out of all device implantations.

Patients and ICD characteristics

The majority of patients (80% men, mean age 62 (SD 13) years) had ischemic heart disease (62%) and a poor LVEF (33±15%) (Table 1). At implantation, QRS duration (124±37 ms) and renal clearance (79±38 ml/min) were measured. At discharge, patients were using beta-



blockers (54%), ACE inhibitors/AT II antagonists (75%), diuretics (62%), aspirin (40%) and oral anticoagulants (50%). Implanted first ICDs were single chamber devices (n=335, 14%), dual chamber devices (n=1171, 48%) or cardiac resynchronization therapy-defibrillators (CRT-Ds) (909, 38%).

Incidence and causes of surgical re-intervention

During 7632.3 ICD-years of follow-up, 145 surgical re-interventions were required in 122 (3.9%) patients. Median time to first re-intervention was 75 days (interquartile range, 14 to 258 days).

Cumulative incidence of first surgical re-intervention after the most recent ICD implantation was 3.5% (95% CI 2.9-4.1%) after one year, 4.3% (95% CI 3.5-5.1%) after two years and 4.7% (95% CI 3.9-5.5%) after three years. Over-all the event-rate of a surgical re-intervention was 1.9 (95% CI 1.6-2.2) per 100 ICD-years.

Table 1. Patient characteristics at first ICD implantation.

	Patients (n=2415)
Clinical characteristics	
Age, mean (SD), years	62 (13)
Male sex (%)	1921 (80)
Primary indication (%)	1504 (62)
Ejection fraction (%)	33 (15)
QRS, mean (SD), ms	124 (37)
Renal clearance, mean (SD), ml/min	79 (38)
Device type	
Single chamber (%)	335 (14)
Dual chamber (%)	1171 (48)
CRT-D (%)	909 (38)
Medication	
Beta-blocker (%)	1291 (54)
Sotalol (%)	333 (14)
ACE inhibitors/AT II antagonist (%)	1806 (75)
Calcium antagonist (%)	220 (9)
Diuretics (%)	1506 (62)
Statins (%)	1395 (58)
Nitrates (%)	430 (18)
Amiodarone (%)	454 (19)
Aspirin (%)	961 (40)
Oral anticoagulants (%)	1217 (50)

CRT-D = cardiac resynchronization device-defibrillator

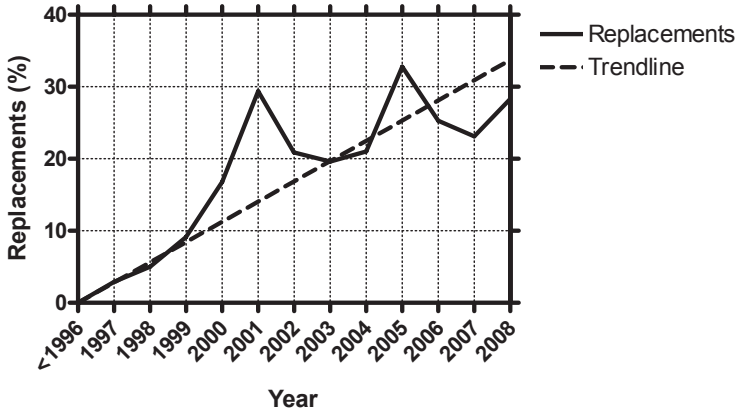


Figure 1. Annual percentage of replacements out of all implanted ICDs (solid line) and trend line (dashed line).

Ninety-five (66%) re-interventions were due to an infectious cause and the remaining 50 (34%) were due to a non-infectious cause (Table 2). Infectious causes were pocket infections (57, 60%) and decubic ulcers, requiring explantation (11, 12%) or relocation (27, 28%). Hematoma, requiring evacuation was the most common (31, 21%) non-infectious cause for surgical re-intervention. Calculated event rate for the occurrence of surgical re-intervention was 1.2 (95% CI 1.0-1.5) per 100 ICD-years for infectious cause and 0.7 (95% CI 0.5-0.9) per 100 ICD-years for non-infectious cause.

Table 2. Causes for surgical re-intervention.

	All ICDs (n=3161)	First ICD (n=2415)	Replacement ICD (n=746)
Infectious cause			
Pocket infection leading to explantation	57/57	38/38	19/19
Decubic ulcer leading to explantation	11/11	7/7	4/4
Decubic ulcer leading to relocation	27/22	11/9	16/13
Non-infectious			
Hematoma requiring evacuation	31/29	24/24	7/5
Device migration leading to relocation	10/10	3/3	7/7
Pain complaints of the patient leading to relocation	9/7	7/6	2/1
Total infectious causes	95/81*	56/47*	39/34*
Total non-infectious causes	50/45*	34/32*	16/13*
Total	145/122*	90/77*	55/45*

*Since multiple re-interventions could have been required in a single ICD treatment, the number of different ICDs does not add up to the total.

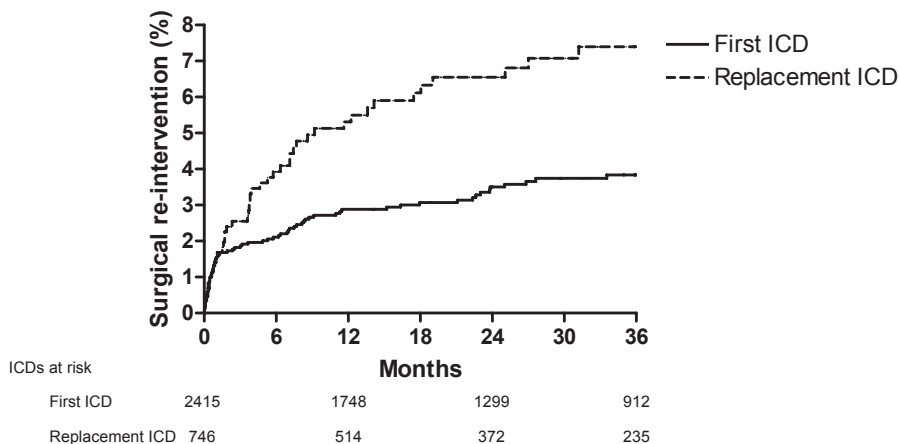


Figure 2. Kaplan-Meier curve for first surgical re-intervention, first implanted ICD vs. replacement ICD.

First implanted ICD vs. replacement ICD

In the first implanted ICD group (2415, 76%), 90 surgical re-interventions were required in 77 different ICDs during a summed follow-up of 5949 ICD-years. The 746 (34%) replacement ICDs required 55 surgical re-interventions in 45 patients during a summed follow-up of 1683 ICD-years.

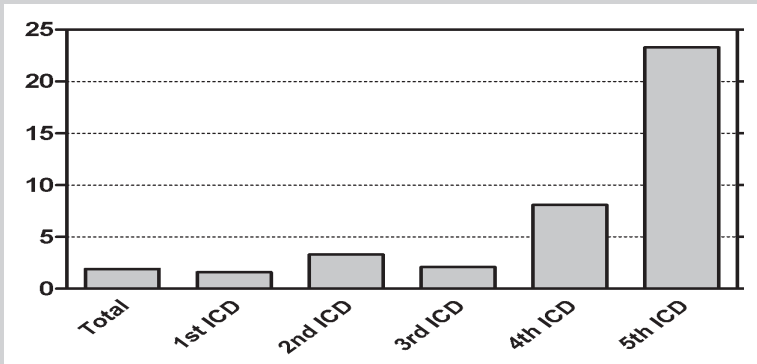
As shown in Figure 2, three years cumulative incidence of first surgical re-intervention was 3.9% (95% CI 3.1-4.7%) for first implanted ICDs and 7.5% (95% CI 5.3-9.7%) for replacement ICDs. The calculated event-rate per 100 ICD-years was 1.5 (95% CI 1.2-1.9) for the first implanted ICDs and 3.3 (95% CI 2.5-4.3) for replacement ICDs, corresponding to a more than doubled (rate ratio 2.2 [95% CI 1.5-3.0, p<0.001]) requirement for surgical re-intervention in replacement ICDs.

Further stratification demonstrated an event-rate of surgical re-intervention for an infectious cause of 0.9 (95% CI 0.7-1.2) per 100 ICD-years in first implanted ICDs and 2.3 (95% CI 1.6-3.2) per 100 ICD-years in replacement ICDs. Per 100 ICD-years, the need for surgical re-intervention for non-infectious causes was 0.6 (95% CI 0.4-0.8) in first implanted ICDs and 1.0 (95% CI 0.5-1.5) in replacement ICDs. When comparing replacement ICDs with first implanted ICDs, the calculated rate ratios are 2.5 (95% CI 1.6-3.7, p<0.001) for infectious causes and 1.7 (95% CI 0.9-3.0, p=0.09) for non-infectious causes.

As is shown in Table 3, further sub-division in the consecutive number of ICD replacements, shows an increase in the need for surgical re-intervention with every consecutive ICD replacement. Event-rates per 100 ICD-years range from 1.5 (95% CI 1.2-1.9) in the first implanted ICD, to 8.1 (95% CI 1.7-18.3) in the fourth implanted ICD.

Table 3. Requirement for re-intervention per consecutive implanted ICD.

	Total	1st ICD	2nd ICD	3rd ICD	4th ICD	5th ICD
Number of ICDs	3161	2415	609	107	24	6
Events	145	90	46	5	3	1
Total years implanted	7632.3	5949	1406	236	37	4.3
Events per 100 ICD-years (95% CI)	1.9 (1.6 – 2.2)	1.5 (1.2 – 1.9)	3.3 (2.4 – 4.4)	2.1 (0.7 – 4.9)	8.1 (1.7 – 18.3)	23.3 (0.6 – 129.6)



DISCUSSION

In this assessment of the requirement of pocket related surgical re-interventions after ICD treatment, the findings can be summarized as follows: 1) The three years cumulative incidence of first surgical re-intervention in all implanted ICDs was 4.7% (95% CI 3.9-5.5%) with an event-rate of 1.9 (95% CI 1.6-2.2) per 100 ICD-years; 2) Replacement ICDs demonstrate a doubled occurrence of surgical re-interventions (rate ratio 2.2 [95% CI 1.5-3.0]); 3) Infectious causes (rate ratio 2.5, 95% CI 1.6-3.7), as well as non-infectious causes (rate ratio 1.7 [95% CI 0.9-3.0, $p=0.09$]) seem to be more frequent in replacement ICDs; 4) The occurrence of surgical re-interventions seem to increase with every consecutive replacement.

Replacements

Since large randomized trials have proven ICD treatment to improve survival in the primary and secondary prevention of sudden cardiac death, worldwide implantation rates have amplified substantially.^{8,9,20} With increased survival of patients and limited service life of the devices, Hauser estimated that over 70% of the currently implanted patients outlive their ICD and therefore requires replacement.¹¹ which is in line with the results of this study. Due to the significant increase of ICD implantations the number of replacements is increasing rapidly. However, with the limited service life of the current devices, it can be expected that replacements will increase drastically and potentially even outnumber first implanted ICDs.¹² Previous studies have described the increasing risk for complications, associated with device replacements.^{11, 13, 21-24} The current study adds to prior literature in that it compares the



event rates in a large population and differentiates in the cause of intervention (infectious or non-infectious) and in the consecutive number of ICD replacements.

Re-interventions

The present study reports differences in the risk of surgical re-interventions between first implanted ICDs and replacement ICDs. In the comparison with previous trials, differences in defining end points should be taken into account. For a decent comparison between first implantation and replacement, the current analysis did not take causes in account that would distort comparison. Therefore, since leads are commonly only implanted at first implantation, lead related complications were not used in the analysis and only pocket related complications were noted.

The most frequent infectious cause for device explantation is cardiac device infection (CDI), a serious and potentially life threatening condition which is associated with significant morbidity and mortality. Additionally, CDI is associated with additional medical costs which have been estimated at an average of \$50.000 per patient.

With the expansion of evidence based indications for cardiac devices the number of device related procedures has rapidly increased over the past decade which also resulted in an increased number of CDI. Furthermore it has been reported that the increase in CDI has outpaced the increase in implantation rate.²⁵ Recent reported rates of CDI vary between approximately 0.5% and approximately 5%.^{13, 14, 24, 26}

It has been hypothesized that local perioperative wound contamination is a major mechanism predisposing to local or systemic pacemaker infection.²⁷ Da Costa et al. evaluated the role of local bacterial flora on pacemaker-related infection and skin erosion and concluded that their results strongly support this hypothesis.²⁶ Furthermore, it has been reported that device revision procedures (generator exchange / lead related procedure) are associated with CDI. Gould and Krahn reported that ICD generator replacement in patients with advisory devices is associated with a substantial rate of infectious complications (1.9% after a mean follow up of 2.7 months). Furthermore it should be taken in account that the consequences of an early re-intervention for a non-infectious cause can be considered more harmful than the underlying complication itself.¹⁵ In their recent paper Lekkerkerker et al. reported that device revisions are an important risk factor for CDI with an odds ratio of 3.67 (95% CI 1.51 to 8.96, $p < 0.01$) for any device related revision procedure, or an odds ratio of 2.47 (95% CI 1.25 to 4.87, $p < 0.01$) for a generator exchange and an odds ratio of 6.67 (95% CI .33 to 33.49, $p = 0.02$) for a lead related intervention.¹⁴ Furthermore Klug and co-workers also described an odds ratio of 2.2 for generator replacements, after 12 months follow-up in 6319 implanted devices, of which 1854 being replacement devices.¹³ In the current study, during 7623.3 ICD-years of follow-up, per 100 ICD-years, the need for surgical intervention for infectious causes was 0.6 (95% CI 0.4-0.8) in first implanted ICDs and 1.0 (95% CI 0.5-1.5) in replacement ICDs. When comparing replacement ICDs with first implanted ICDs, the corresponding rate ratio was 2.5 (95% CI 1.6-3.7, $p < 0.001$).

Considering the above, the need for device replacement should be reduced to a minimum and all effort should be made to improve device longevity.

CONCLUSION

Replacement ICDs demonstrated a doubled occurrence of pocket related surgical re-interventions when compared to first implanted ICDs. Furthermore, both the requirement for surgical re-intervention due to infectious cause and non-infectious cause seemed to be increased in replacement ICDs and the requirement for re-intervention increased with every consecutive replacement. Therefore, every effort should be addressed to improve ICD



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