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Long term complications in patients implanted with subcutaneous implantable defibrillators

Real-world data from the Extended ELISIR experience

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ABSTRACT

Background. Recently, the Food and Drug administration issued a recall for the subcutaneous implantable cardioverter defibrillator (S-ICD) due to the possibility of lead ruptures and accelerated battery depletion.

Objective. Aim of this study is to evaluate device-related complications over time in a real-world multicentered large S-ICD cohort.

Methods. Patients implanted with S-ICD from January 2015 to June 2020 were enrolled from a 19 institution European registry (ELISIR NCT0473876). Device-related complication rates over follow-up were collected. Last follow-up of patients was performed after the Boston Scientific recall issue.

Results. A total of 1254 patients (52.0 [41.0–62.2] years, 77.6% male, 30.9% ischemic) was enrolled. Over a follow-up of 23.2 [12.8–37.8] months, complications were observed in 117 (9.3%) patients, for a total of 127 device-related complications (23.6% managed conservatively, 76.4%) requiring reintervention). Twenty-seven (2.2%) patients had an unanticipated generator replacement, after 3.6 [3.3–3.9] years, while 4 (0.3%) had a lead rupture. BMI (HR 1.063 [1.028–1.100]; p=0.000), chronic kidney disease (HR 1.960 [1.191–3.225]; p=0.008), and oral anticoagulation (HR 1.437 [1.010–2.045]; p=0.043) were associated with an increase of overall complications whereas older age (HR 0.980 [0.967–0.994]; p=0.007) and procedure performed in high volume centers (HR 0.463 [0.300–0.715]; p=0.001) were protective factors.

Conclusion. The overall complication rate over 23.2 months of follow-up in a multicentered S-ICD cohort was 9.3%. Early unanticipated device battery depletions occurred in 2.2% of patients, while lead fracture was observed in 0.3%, in line with the expected rates reported from Boston Scientific.

Keywords: sub-cutaneous implantable cardioverter defibrillator; S-ICD; device complications; device recall; lead complications.

INTRODUCTION

In recent times, the subcutaneous implantable cardioverter defibrillator (S-ICD) has become a valid alternative to the transvenous implantable cardioverter defibrillator (TV-ICD) for sudden cardiac death (SCD) prevention. Despite their life-saving role, TV-ICD are associated with short- and long-term complications leading to considerable morbidity and mortality, such as lead failure and infections[1,2]. If TV-ICD related infection rates may vary between 0.67% and 1.49% over a 3- to 12-month follow-up period[3], lead failure rates significantly differ according to the lead type, the year of implantation (with older leads more likely to fail) and the follow-up duration. Indeed, if the Riata[4] and the Fidelis[5] leads have shown the highest rates of lead failure (up to 25%) and they have thereby been recalled, when assessing of the most used leads (Durata, Endotak Reliance, Sprint Quattro Secure, Linox), the estimated rates of freedom from lead failure at 5-year ranged from 97.7% to 98.9%[6]. In this analysis, the authors used lead replacement as a surrogate for lead failure, that may indeed have led to an underestimation of total lead failure events. In a recent metanalysis, including Fidelis, Riata, Durata, Endotak and Quattro leads, an overall incidence of lead failure (% per/year) of 2.23%, 1.17%, 0.45%, 0.36% and 0.29%, was reported, respectively[7].

Although S-ICDs have failed to show lower rates of infection and are associated with a higher risk of pocket complications, they have been extensively used in recent years due to a lower rate and a safer management of lead and major procedure-related complications[1,8], as well as to an easier management of both, especially in the event of lead extraction[9,10]. Recently, Boston Scientific Inc. (*Marlborough, Massachusetts, USA*) recalled the S-ICD subcutaneous electrode (Model 3501) because of the risk of fractures at a specific level (distal to the proximal sense ring). Twenty-seven cases of lead body fractures at this location have been reported, with 1 death as a result of that specific lead complication; although the S-ICD generator and electrode were not returned for a post-mortem analysis, a contributing role related to malfunctioning could not be excluded[11]. Moreover, the manufacturer identified approximately 38,350 active S-ICDs (models A209 and A219) with a certain likelihood of a low voltage capacitor causing accelerated battery depletion as

well as of moisture entrance into the S-ICD generator, potentially causing a short-circuit when the device delivers high voltage shocks. Thus, the Food and Drug administration (FDA) has identified this recall as a Class I recall[12]. Nevertheless, to date, no independent real-world analysis has been run on S-ICD related complications. Therefore, aim of this study is to evaluate all device-related complications over time, as well as the need for re-interventions to manage them.

METHODS

The ELISIR project (Experience from the Long-term Italian S-ICD registry; ClinicalTrials.gov Identifier NCT0473876) is a multi-center, open-label, independent, and physician-initiated observational registry. At the time of this manuscript drafting, 19 Public and Private Healthcare Institutions from 4 different countries in Europe were involved in the registry. The project was approved by each institutional review board and drafted in accordance with the tenets of the Helsinki Declaration.

Registry population and data collection

From January 2015 to June 2020, all consecutive patients undergoing implantation of an S-ICD device were retrospectively enrolled in the registry. For every patient enrolled, demographics and baseline data comprising of cardiovascular risk factors, arrhythmic substrate, peri-procedural data, device programming, and outcome data were collected. For patients undergoing defibrillation testing (DT), ventricular fibrillation (VF) was induced using transthoracic 50 Hz burst pacing. No specifics regarding shock energy and the use of either general anesthesia or deep sedation for the procedure were given. In all patients for whom a post-implant 2-views chest X-ray was available, the PRAETORIAN score was calculated and patients were classified having a low-, intermediate-, or high-risk for conversion failure according to the score definition[13].

Follow-up and outcome definition

Follow-up strategy was left to each center's policy, with most patients being evaluated at 1-, 6-, 12-months, and every 6 months thereafter. Remote device monitoring was used if accepted by each country regulatory policy; all patients provided specific informed consent. All device-related complications were collected over the entire follow-up period, as well as the need for reinterventions to manage them and the subsequent length of hospital stay. As per registry protocol, complications were defined as follows: major pocket hematoma requiring a transfusion or a pocket revision; pocket

infection; air entrapment causing inappropriate shocks; lead displacement impacting device functioning and requiring reintervention; lead fracture; lead infection; device extraction; device replacement for excessive inappropriate shocks; unexpected early battery depletion (defined as within 5 years from implantation in patients with a low arrhythmic burden at follow-up); and unexpected pneumothorax. Early complications were defined as any of the aforementioned complication presenting within the first 48 hours following device placement. Arrhythmia episodes and therapy delivered, either appropriate or inappropriate, were collected during follow-up. Cardiovascular and total mortality were also documented. The primary outcome of the study was defined as the occurrence of any device-related complication since implantation through the entire follow-up. As secondary analysis, the following outcomes were assessed: freedom from sustained ventricular arrhythmic events; freedom from inappropriate shocks; rate of ineffective shocks; overall mortality.

Event definition

An appropriate shock was defined as a therapy delivered because of correctly diagnosed shockable rhythm. An inappropriate shock was defined as shock delivered due to: 1) a supraventricular (SV) tachycardia; 2) oversensing of either cardiac or non-cardiac signals; 3) any other cause resulting in device shock in the absence of a clinical arrhythmia. An ineffective shock was defined as a shock delivered on an adequately recognized shockable rhythm, ineffective to terminate VT/VF. An untreated arrhythmia was defined as VT/VF not treated by the device due to: 1) undersensing of the cardiac signal during VT/VF; 2) misclassification of VT/VF due to the device discrimination algorithm; 3) VT/VF presenting at a lower rate than the cutoff value for device intervention, as established by defibrillator programming.

Predictors definition

S-ICD implantation learning curve was considered completed after the placement of 10. A center was considered a high-volume center after the performance of 13 procedure/year for at least three year in a row[14].

Statistical analysis

All analysis were performed using STATA v. 14.0 (StataCorp LLC, College Station, TX). Continuous variables were expressed as mean±standard deviation (s.d.) if normally distributed or as median [inter-quartile range (IQR)]. Categorical variables were expressed as count (percentage). Comparisons between categorical variables were performed using the Exact Chi-Square or Fisher's Exact test, as appropriate. Associations between predictors and time-dependent outcomes were tested using univariate Cox regression models; time intervals were set as time elapsed from device implantation to either the event or the last available follow-up. A parsimonious model including only variables reaching a $p<0.10$ at univariate analysis was built, to adjust for confounders. Event-free survival and cumulative complication rates were reported using Kaplan-Meier curves. All two-tailed p values <0.05 were considered significant.

RESULTS

Patient population

A total of 1254 patients were enrolled in the current study. The median age of the population at device implant was 52.0 [41.0–62.2] years, with 77.6% of patients being male. Device implantation occurred as primary prevention of SCD in 786 (62.7%) patients of the cohort. Most implantation procedures were performed using the two-incision technique (90.3%). The devices were most commonly placed in an inter-muscular position between the musculus serratus anterior and the musculus latissimus dorsi (81.1%). Adequate post-procedural radiological imaging to assess the PRAETORIAN score was available in 836 (66.6%) patients. The vast majority of the cohort showed a low risk of conversion failure (n=679). Baseline characteristics of the cohort are reported in **Table1**. Peri-procedural characteristics have been reported in Table S The median follow-up of the study was 23.2 [12.8–37.8] months. Complete follow-up data are shown in **Table2.**

Primary outcomes

The primary outcome was observed in 117 (9.3%) patients, for a total of 127 device-related complications; 30 (23.6%) of these were managed conservatively, while the remaining 97 (76.4%) required a reintervention (**Figure1**). Pocket-associated complications were the most common (n=54), pocket hematoma representing 25.2% of the overall complications. A total of 27 patients (2.2%) had unanticipated generator replacement, after a median of 3.6 [3.3–3.9] years. Overall complications were evenly distributed when the investigated cohort was split into a young and old patient subgroup (9.8% vs 5.6% respectively, p=0.108). High-volume centers presented lower rates of complications than non-high-volume centers (8.5% vs 12.8%, p=0.041) (**Figure2)**. BMI (adjusted hazard ratio, aHR 1.063 [1.028–1.100]; p<0.001), chronic kidney disease (CKD) (aHR 1.960 [1.191–3.225]; p=0.008), and the use of oral anticoagulation (aHR 1.437 [1.010–2.045]; p=0.043) resulted significantly associated with an increased risk of any complication at follow-up, while an older age (aHR per year 0.980 [0.967–0.994]; p=0.007) and the performance of the

procedure in a high-volume center (aHR 0.463 [0.300–0.715]; p=0.001) resulted protective factors. When assessing individually infective and non-infective S-ICD complications instead, CKD (aHR 2.436 [1.057–5.615], p=0.037), and the development of a pocket hematoma (aHR 6.075 [2.426–15.207], p<0.001) were associated with infective complications, while a higher BMI (aHR 1.059 [1.014–1.105], p=0.009), use of oral anticoagulation (aHR 1.738 [1.207–2.505], p=0.003), and the procedure being performed at a high-volume center (aHR 0.315 [0.182–0.547], p<0.001) were predictors of non-infective complication. **Table3** summarizes the entire univariate and multivariate cox regression analysis. **Figure3** represents graphically univariate analysis for predictors of overall and by-type complications.

Secondary outcomes

One hundred-eighteen (9.4%) patients received at least one appropriate shock. Arrhythmia-free survival being is shown in **FigureS1**. A total of 12 ineffective shocks were observed, with multiple shocks required for arrhythmia termination in 8 patients, and 4 requiring resuscitation maneuvers and external defibrillation. In the study cohort, 112 (8.9%) patients received inappropriate shocks during the study follow-up. T-wave oversensing (4.4%), muscle noise (1.4%), and AF episodes (1.4%) were the most common triggers of inappropriate shocks. Overall mortality in the registry was 3.4%, end-stage heart failure being the leading cause (1.5%). No device-related deaths were observed. Regression for all other secondary outcomes have been reported in **TableS2**.

DISCUSSION

This is the first large independent multicentered cohort study assessing S-ICD complications in the real-world setting after the issue of the Boston Scientific recall by the FDA[11,12].

The main results from our study are as follows:

- Over a median follow-up time of 23.2 months, 9.3% of patients experienced device-related complications. Pocket related complications were the most common, with pocket hematoma representing the leading one.
- The rate of unanticipated generator replacement was 2.2%, with a median replacement time below 4 years. Four patients (0.3%) experienced a lead fracture, requiring lead replacement.
- Management of all device-related complications was safe, with no device-related deaths observed.
- One hundred-eighteen (8.9%) patients experienced inappropriate shocks, with T-wave oversensing and atrial fibrillation representing the most common triggers. Advanced age and the use of the SMART PASS algorithm resulted protective factors from inappropriate shocks.
- Younger age, higher BMI, CKD, and the chronic use of oral anticoagulants were the main predictors for all complications at follow-up. Procedure performance in a high-volume center resulted associated with a significant reduction in overall complications.

Device or lead-related complications and the current FDA recall

Long-term complications in TV-ICD are currently estimated around 5%, with infections and lead-related adverse events being the most common[15]. TV-ICD infectious or lead-related complications might result in endocarditis or lead extraction, with non-negligible mortality rates, especially with older devices. The S-ICD technology was indeed developed specifically to reduce device-related complications, and to manage these issues more easily. Although the peri-procedural complication rate resulted close to 10% for unexperienced operators, a halving of the complication rates after the initial learning curve phase was observed. In our analysis, the S-ICD complication rate at follow-up

resulted noteworthy (9.3%), similar to TV-ICD but, as expected, with a much more favorable outcome profile, with no device-related deaths being reported, though hospitalization and reinterventions were required. Patients requiring lead extraction and repositioning did not experience significant post-operative consequences. Differently from the report of *Knops* et al. on peri-procedural complications[14], the overall long-term complications had no trend towards improvement with operators' experience in our study, while overall center volume seemed to have a significant impact, especially on non-infective complications. Indeed, we hypothesize that center's volume importance extends beyond the simple number of procedures performed by the single operator, but also accounts for more experience scrub teams, better peri-procedural flow, and a proactive hospital in-ward environment. Our data seems to strongly point towards the centralization of S-ICD procedures into high-volume centers to reduce overall complications and related downsides.

In addition to the crude complication rate, the type of complications should be discussed as well. The PRAETORIAN trial showed comparable complication rates between S-ICD and TV-ICD, with subcutaneous devices presenting more surgical complications and transvenous devices presenting more lead related complications[16]. Our study partially confirmed these findings. The main reasons for S-ICD complications in our study were indeed surgical, with pocket complications resulting the most frequent. However, we also detected a non-negligible number of lead-related complications, with around 20% of all complications being lead related. We observed a similar rate of lead fracture to that declared in the medical device advisory recently published by Boston Scientific (0.3%)[11], alongside several lead dislodgements and infections (**Figure4**). Until recently, the S-ICD lead reliability was proposed as the cornerstone for its broad clinical adoption, with only rare case reports of lead-associated complications. However, despite the reported fractures, the long-term performance of S-ICD leads still remains significantly better than endovascular leads[10,17]. Additionally, the big advantage of S-ICDs over TV-ICDs is represented by the relative safety with which leads can be explanted and replaced, with virtually no mortality risk for the patient.

Our results also confirmed the rate of premature battery depletion predicted by the medical device advisory[12], with 2.2% of EMBLEM S-ICD devices requiring an unanticipated replacement. In a single center cohort, *Ip*[18] reported a prevalence of 3.4% of premature battery failure in his cohort, occurring at an average of 1095 days, in a cohort extending beyond the initial advisory subset. We report slightly lower battery depletion rates at follow-up, in a larger dataset of patients.

Inappropriate shocks

The number of patients experiencing inappropriate shocks in our study was 9.4% at almost 2 years of follow-up. The leading cause was T-wave oversensing and an important age-dependency was observed (**FigureS2**). This high rate of inappropriate shocks was unexpected, considering the device setting of VT/VF cutoff, and the availability of the smart pass algorithm in 85% patients. Our results were similar to first S-ICD release reported in the EFFORTLESS study, but higher when compared to the inappropriate shocks reported in the PRAETORIAN trial[16,19]. Despite the efforts made in trying to better set the devices and improve the discrimination algorithms, inappropriate shocks remain a relevant S-ICD complication, differently from TV-ICD, where the programming optimization led to a clear reduction of oversensing-related inappropriate shocks over the years[20]. Nevertheless, it should be underlined that SV tachycardia still represent the leading cause of inappropriate shocks in TV-ICD, while it seem to have a lower weight in the S-ICD system[1].

Complication predictors

The strongest overall predictor for any device-related complication at follow-up in our cohort was CKD. As expected, CKD was mostly associated with infective complications (**Table3**). Our findings may appear partially in contrast with the report of *El Chami* et al, who showed that patients on hemodialysis may actually be safely treated with S-ICDs, since the complication rate was similar to the general population of S-ICD recipients (7.9%)[21]. Nevertheless, both experiences reported overall complication rates within comparable ranges, far lower than those reported in TV-ICDs recipients

with CKD and hemodialysis[22,23]. This underlines the importance of using a completely extravascular system for these patients (especially if on hemodialysis), being the S-ICD the best option for these patients in absence of the need for pacing.

A higher BMI was also associated with a higher complication rate, impacting both infective and non-infective ones. This finding is not unexpected: an excess of subcutaneous adipose tissue may interfere with the correct placement of both the lead and the generator of the S-ICD, potentially leading to higher rates of lead/generator displacements. Additionally, the creation of an adequate pocket in patients with a higher BMI may result challenging, potentially exposing to a higher risk of pocket hematomas and/or infections. An elevated BMI has also been associated with more ineffective shocks and a lower effectiveness of the S-ICD device, and it is an important correction factor of the PRAETORIAN score[13,24,25]. Given all these findings, the use of S-ICD devices in morbidly obese patients should be carefully evaluated and TV-ICD may be beneficial in some cases.

Finally, it should be noted that pocket hematomas were very strong predictors of more severe infective complications in an S-ICD recipient, regardless of their conservative management or a reintervention. This finding is in line with what has been observed in TV-ICDs, which presents significantly increased risks of infection requiring hospitalization due to pocket infection, bacteremia or endocarditis after developing clinically relevant pocket hematoma. Our data did highlight a strong *liason* between significant pocket hematomas and subsequent infection for S-ICD, similarly to the 7-fold increased for TV-ICD observed in the BRUISE registry[26].

Limitations

The first limitation is inherently associated to the non-randomized, observational nature of this European, real-world, multicentered registry of unselected patients undergoing S-ICD implantation. Moreover, due to the retrospective nature of our registry, all complications could be not centrally adjudicated by a central committee, and no audit committee that might sample a statistically meaningful number of randomly selected charts to confirm (or deny) that under-reporting

complication was not a significant issue was present. Indeed, also because proceduralist sometimes may under-report their complications, a certain rate of under-reported (or not) complications might have occurred. Nevertheless, most complication are self-evident, easy to define and uncontroversial, such as infective events or lead displacement, while others always require engineering evaluation from the company, with subsequent official report of the issue, thereby providing consistency throughout the entire follow-up.

CONCLUSIONS

In this European multicenter study assessing long-term complications in patients undergoing S-ICD implantation, the overall complication rate was 9.3% during the first two years after implantation. Younger age, higher BMI, CKD, and the use of oral anticoagulants were main predictors for any complication during follow-up. Procedural performance in high-volume centers was associated with a significant reduction in overall complications. In our population, an early unanticipated battery depletion occurred in 2.2% of patients, while lead fracture was observed rarely (0.3%).

Table 1

Baseline Characteristics (n=1254)	
Age (years), median[IQR]	52.0[41.0–62.2]
Male, n(%)	973(77.6)
BMI, median[IQR]	25.0[23.0–28.0]
Diabetes, n(%)	186(16.8)
Hypertension, n(%)	484(38.6)
Sport Practice, n(%)	99(12.3)
CKD, n(%)	209(16.7)
LVEF (%), mean±d.s	43.0±15.9
Primary Prevention Implant, n(%)	786(62.7)
Underlying Cardiac Disease	
Ischemic cardiomyopathy, n(%)	*387(30.9)*
Dilatative cardiomyopathy, n(%)	*283(22.6)*
Hypertrophic cardiomyopathy, n(%)	*115(9.2)*
Arrhyhtmogenic cardiomyopathy, n(%)	*58(4.6)*
Brugada syndrome, n(%)	*125(10.0)*
Idiopathic VF, n(%)	*132(9.6)*
Alcoholic Cardiomyopathy, n(%)	*6(0.4)*
Valvular Cardiomyopathy, n(%)	*37(2.9)*
Other, n(%)	*111(8.8)*
Atrial Fibrillation, n(%)	246(19.6)
Paroxysmal, n(%)	*149(11.9)*
Persistent, n(%)	*55(4.4)*
Permanent, n(%)	*42(3.6)*
Removal of previous TV device, n(%)	153(12.2)
Beta-blockers, n(%)	901(71.8)
Antiarrhythmics IC, n(%)	35(2.8)
Amiodarone, n(%)	148(11.8)

*Percentages were calculated on patients for which the data was available

Table 2

Follow-up data (n = 1254)	
Follow-up time (months), median[IQR]	23.2[12.8–37.8]
Patients experiencing device-related complications, n(%)	117(9.3)
Device-related complications, n(%)	127(100)
Within 48 hours, n(%)	15(11.8)
Not requiring reintervention, n(%)	4(3.1)
Pocket Hematoma, n(%)	1(0.8)
Air entrapment, n(%)	3(2.4)
Requiring reintervention, n(%)	11(8.7)
Pocket Hematoma, n(%)	5(3.9)
Lead displacement, n(%)	5(3.9)
Sub-cutaneous emphysema, n(%)	1(0.8)
After 48 hours, n(%)	112(88.2)
Not requiring reintervention, n(%)	26(20.5)
Pocket-associated complications, n(%)	20(15.7)
Pocket hematoma, n(%)	18(14.2)
Pocket infection, n(%)	2(1.5)
Air Entrapment, n(%)	6(4.8)
Requiring reintervention, n(%)	86(67.7)
Lead-associated complications, n(%)	21(16.5)
Lead displacement, n(%)	5(3.9)
Lead rupture, n(%)	4(3.1)
Lead infection, n(%)	12(9.5)
Pocket-associated complications, n(%)	28(22.0)
Pocket hematoma, n(%)	14(11.0)
Pocket infection, n(%)	14 (11.0)
Unanticipated generator replacement, n(%)	27(21.3)
Excessive inappropriate shocks, n(%)	8(6.9)
Non-infective peri-generator skin erosion, n(%)	2(1.5)
Patients experiencing appropriate shocks, n(%)	118(9.4)
Patients experiencing inappropriate shocks, n(%)	112(8.9)
Reason for inappropriate shock:	
AF, n(%)	17(1.4)
TWO, n(%)	55(4.4)
Myopotentials, n(%)	18(1.4)
Atrial tachycardia, n(%)	3(0.2)
VAD Interference, n(%)	1(0.1)
Lead Problem, n(%)	6(0.5)
Air Entrapment, n(%)	9(0.7)
Twiddler's, (%)	2(0.2)
Patients experiencing ineffective shocks, n(%)	12(1.0)
Deaths, n(%)	42(3.4)
Cardiovascular death, n(%)	29(2.3)

Table 3

Primary combined outcome						
	HR	C.I.	p	aHR	C.I.	p
Age	0.989	[0.978–1.000]	***0.064***	0.980	[0.967–0.994]	**0.007**
Male sex	1.144	[0.725–1.806]	0.562			
Hypertension	0.916	[0.629–1.335]	0.651			
BMI	1.055	[1.021–1.090]	**0.001**	1.063	[1.028–1.100]	**<0.001**
Diabetes	0.767	[0.428–1.374]	0.373			
CKD	1.821	[1.202–2.759]	**0.005**	1.960	[1.191–3.225]	**0.008**
LVEF	1.002	[0.991–1.014]	0.693			
Two incision technique	0.917	[0.548–1.533]	0.741			
Inter-muscular placement	0.729	[0.486–1.095]	0.128			
Patients on OAC	1.391	[1.015–1.905]	**0.040**	1.437	[1.010–2.045]	**0.043**
High Volume Center	0.634	[0.420–0.957]	**0.030**	0.463	[0.300–0.715]	**0.001**
Learning Curve Completed	1.152	[0.714–1.859]	0.561			
Infective complications						
Age	0.982	[0.959–1.005]	0.121			
Male sex	1.625	[0.564–4.686]	0.369			
Hypertension	1.074	[0.501–2.300]	0.854			
BMI	1.064	[0.999–1.132]	***0.052***	1.042	[0.974–1.114]	0.232
Diabetes	1.013	[0.347–2.953]	0.980			
CKD	3.871	[1.830–8.189]	**<0.001**	2.436	[1.057–5.615]	**0.037**
LVEF	0.963	[0.938–0.989]	**0.005**	0.974	[0.948–1.002]	0.070
Two incision technique	0.695	[0.257–1.880]	0.867			
Intramuscular placement	0.809	[0.344–1.903]	0.628			
Patients on OAC	1.284	[0.672–2.453]	0.449			
Pocket Hematoma	7.711	[3.094–19.217]	**<0.001**	6.075	[2.426–15.207]	**<0.001**
High Volume Center	1.464	[0.507–4.226]	0.481			
Learning Curve Completed	0.914	[0.344–2.428]	0.857			
Non-infective complications						
Age	0.994	[0.980–1.009]	0.460			
Male sex	1.167	[0.651–2.093]	0.603			
Hypertension	1.081	[0.674–1.731]	0.746			
BMI	1.051	[1.008–1.095]	**0.018**	1.059	[1.014–1.105]	**0.009**
Diabetes	0.672	[0.306–1.478]	0.323			
CKD	1.843	[1.092–3.114]	**0.022**	1.504	[0.844–2.682]	0.166
LVEF	0.999	[0.985–1.015]	0.995			
Two incision technique	0.743	[0.380–1.452]	0.385			
Intramuscular placement	0.615	[0.369–1.026]	***0.063***	0.744	[0.416–1.334]	0.322
Patients on OAC	1.645	[1.182–2.286]	**0.003**	1.738	[1.207–2.505]	**0.003**
High Volume Center	0.457	[0.279–0.746]	**0.002**	0.315	[0.182–0.547]	**<0.001**
Learning Curve Completed	0.894	[0.488–0.639]	0.717			

FIGURE LEGENDS

Figure 1: Cumulative incidence of primary outcome (complication rate) over time.

Figure 2: Complication rate distribution by age (70+ and <70 y.o.) and by center volume. *Cons=conservative.*

Figure 3: Univariate predictors of overall (red), non-infective (teal), and infective complications (blue).
BMI=body mass index; CKD=chronic kidney disease; HTN=hypertension; HVC=high-volume center; LC=learning curve; LVEF=left ventricular ejection fraction; OAC=oral anti-coagulation; TIT=two-incision technique.

Figure 4: Lead extraction after lead fracture in an S-ICD patient.

Figure 1

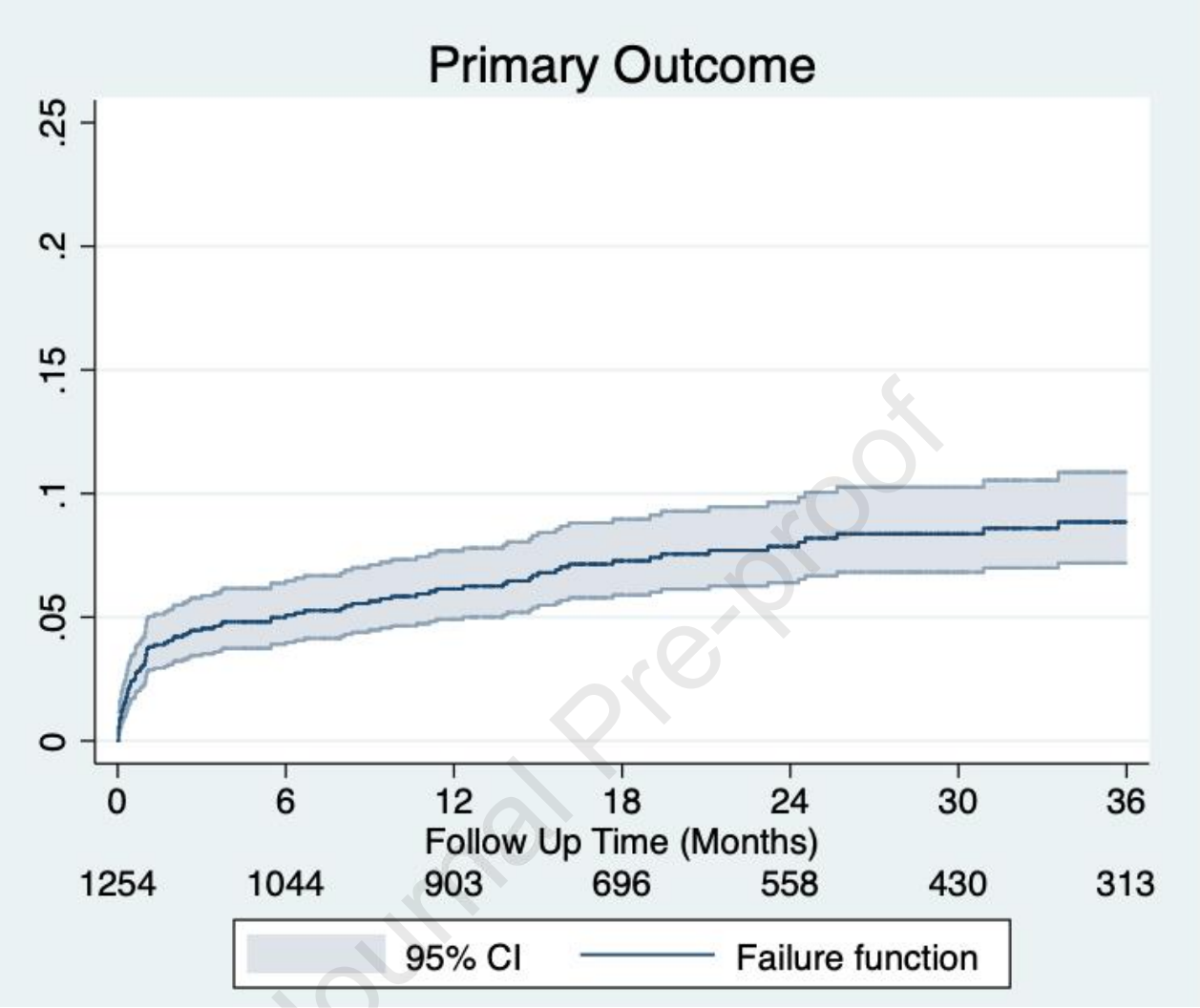


Figure2

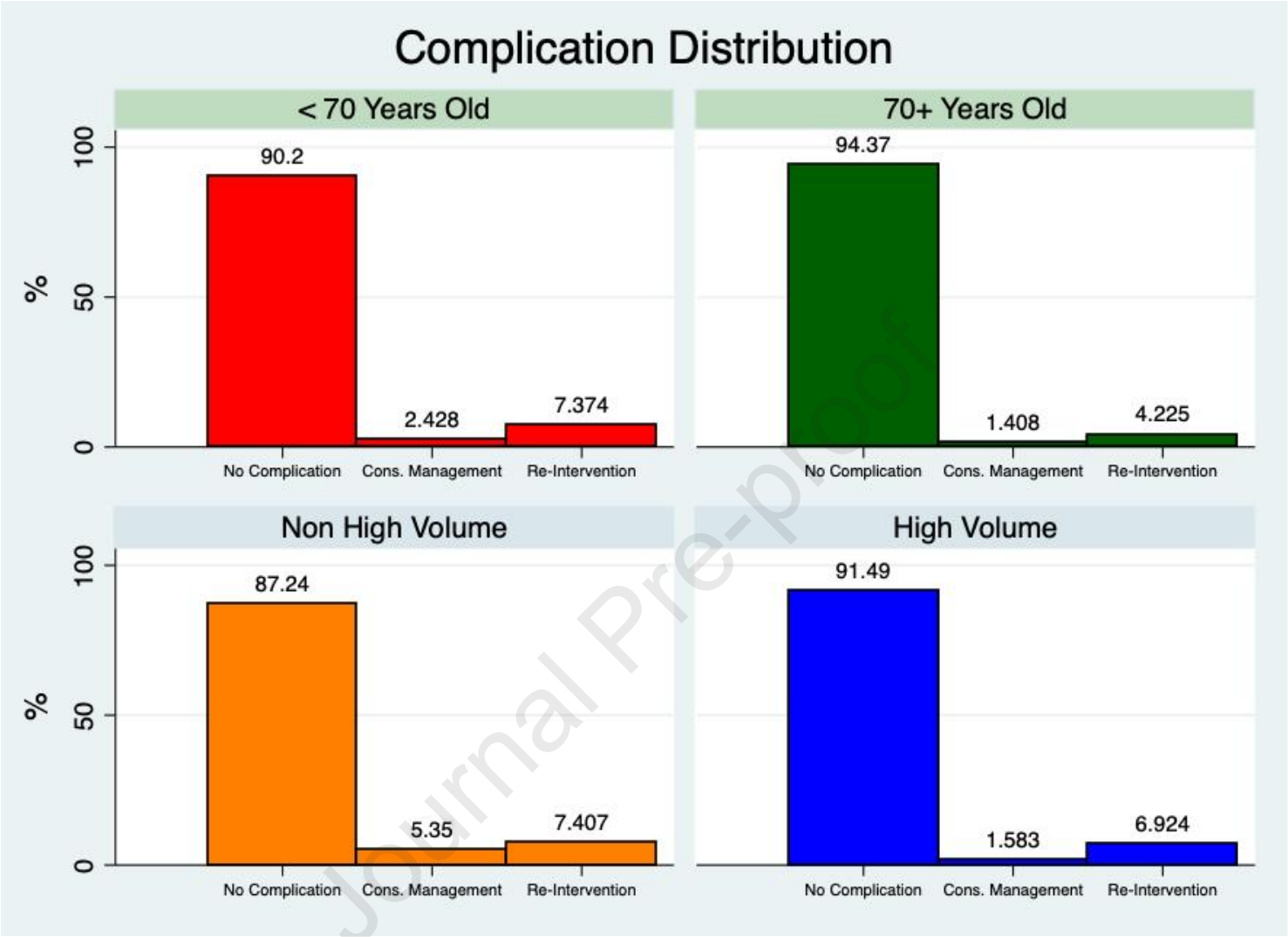


Figure3

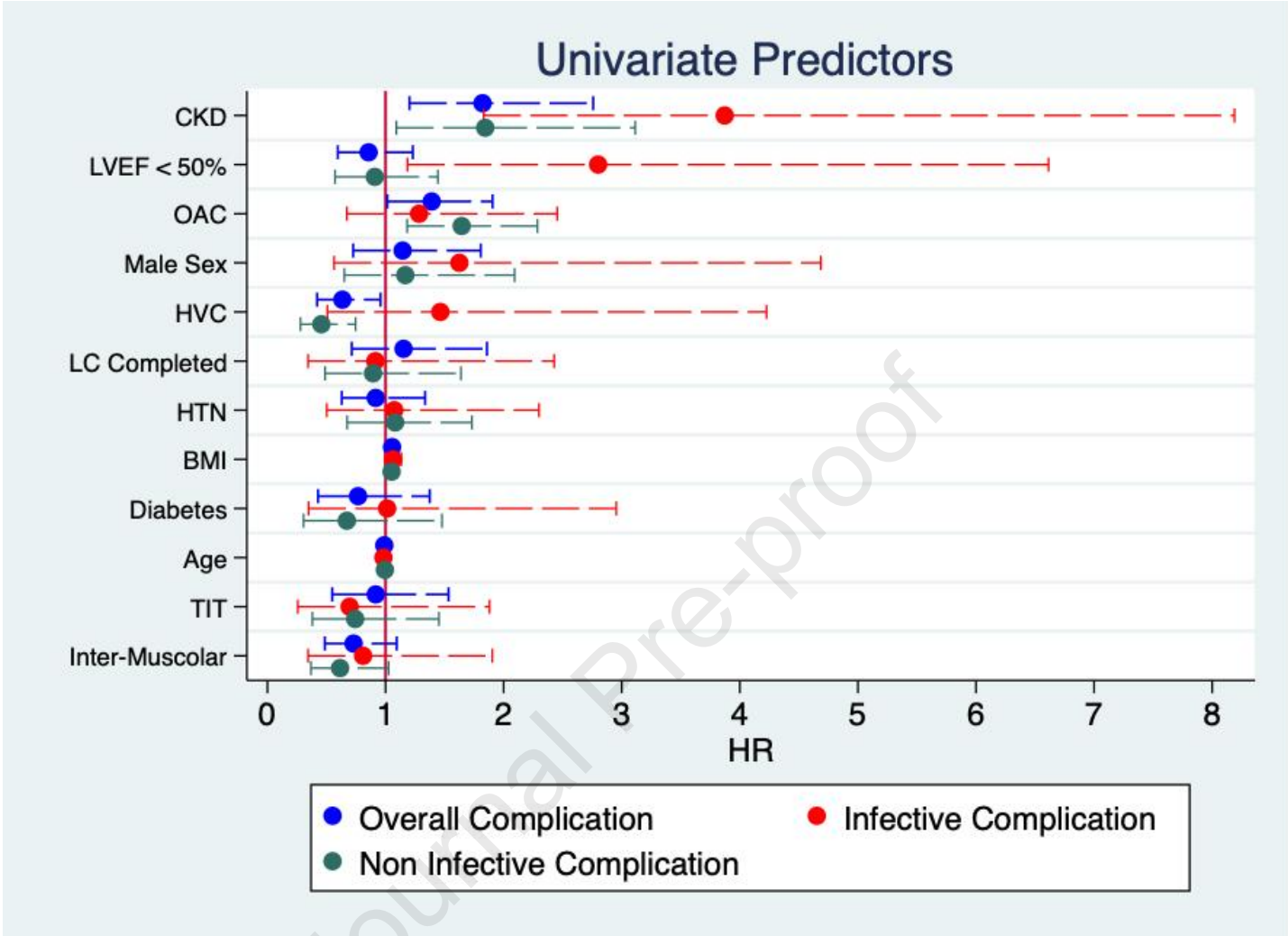
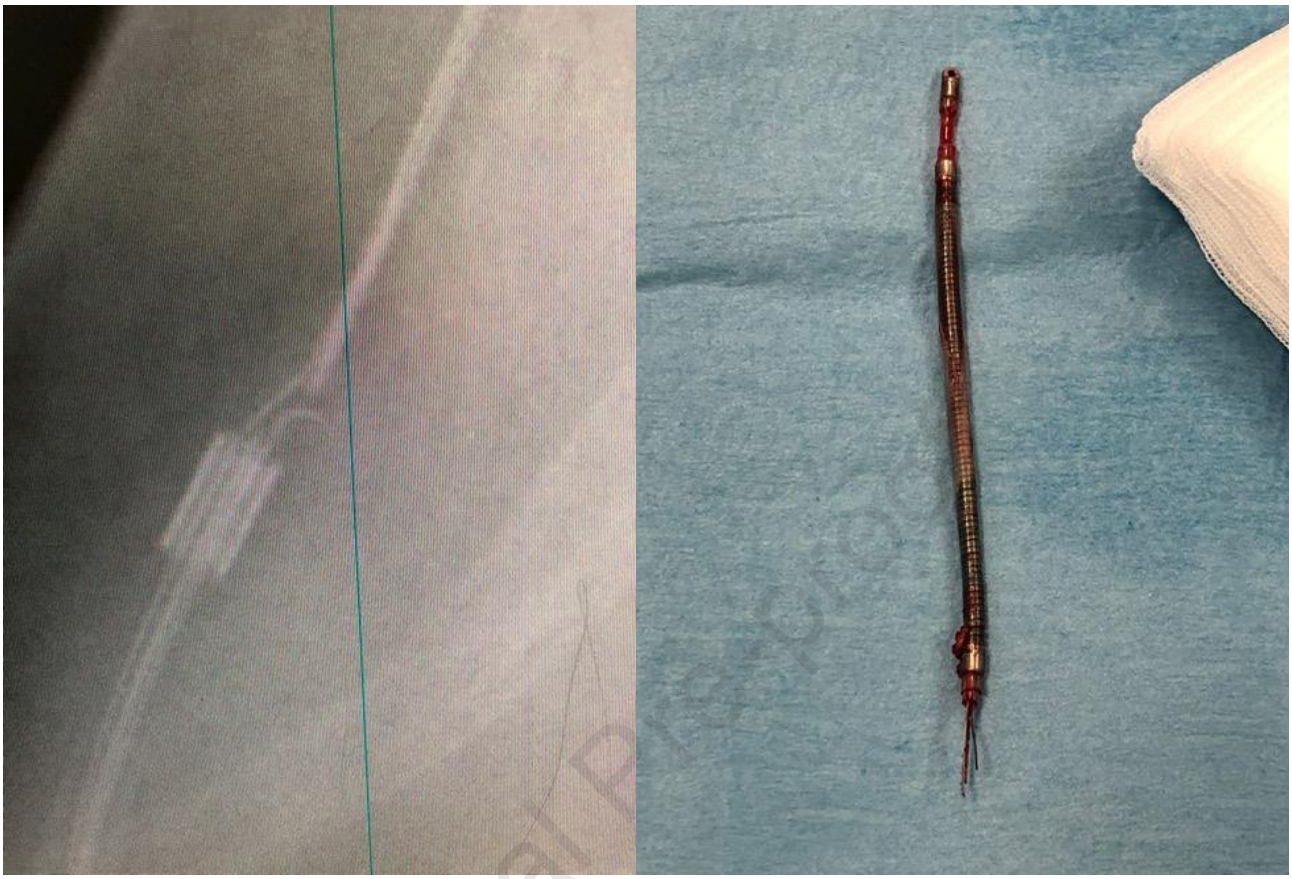


Figure 4



REFERENCES

1. Basu-Ray I, Liu J, Jia X, et al.: Subcutaneous Versus Transvenous Implantable Defibrillator Therapy: A Meta-Analysis of Case-Control Studies. JACC: Clinical Electrophysiology 2017; 3:1475–1483.
2. Kirkfeldt RE, Johansen JB, Nohr EA, Jorgensen OD, Nielsen JC: Complications after cardiac implantable electronic device implantations: An analysis of a complete, nationwide cohort in Denmark. European Heart Journal 2014; .
3. Peterson PN, Varosy PD, Heidenreich PA, et al.: Association of single- vs dual-chamber ICDs with mortality, readmissions, and complications among patients receiving an ICD for primary prevention. JAMA - Journal of the American Medical Association 2013; 309:2025–2034.
4. Hauser RG, McGriff D, Retel LK: Riata implantable cardioverter-defibrillator lead failure: Analysis of explanted leads with a unique insulation defect. Heart Rhythm 2012; 9:742–749.
5. Hauser RG, Hayes DL: Increasing hazard of Sprint Fidelis implantable cardioverter-defibrillator lead failure. Heart Rhythm 2009; 6:605–610.
6. Zeitler EP, Selzman KA: Defibrillator Lead Survival: Where Is the Threshold? Circ: Cardiovascular Quality and Outcomes [Internet] 2020 [cited 2021 Jun 16]; 13. Available from: https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.120.006649
7. Providência R, Kramer DB, Pimenta D, et al.: Transvenous Implantable Cardioverter-Defibrillator (ICD) Lead Performance: A Meta- Analysis of Observational Studies. JAHA [Internet] 2015 [cited 2021 Jun 16]; 4. Available from: https://www.ahajournals.org/doi/10.1161/JAHA.115.002418
8. Rordorf R, Casula M, Pezza L, et al.: Subcutaneous versus transvenous implantable defibrillator: An updated meta-analysis. Heart Rhythm 2020; .
9. Behar N, Galand V, Martins RP, et al.: Subcutaneous Implantable Cardioverter-Defibrillator Lead Extraction: First Multicenter French Experience. JACC: Clinical Electrophysiology 2020; 6:863–870.
10. Mitacchione G, Schiavone M, Gasperetti A, Viecca M, Curnis A, Forleo GB: Neglected lead tip erosion: An unusual case of S-ICD inappropriate shock. Journal of Cardiovascular Electrophysiology 2020; .
11. Boston Scientific Recalls EMBLEM S-ICD Subcutaneous Electrode (Model 3501) Due to Risk of Fractures | FDA [Internet]. [cited 2021 Feb 21],. Available from: https://www.fda.gov/medical-devices/medical-device-recalls/boston-scientific-recalls-emblem-s-icd-subcutaneous-electrode-model-3501-due-risk-fractures
12. Boston Scientific Corporation Recalls EMBLEM S-ICD (Subcutaneous Implantable Cardioverter Defibrillator) System Due to Risk of Short-Circuit | FDA [Internet]. [cited 2021 Feb 21],. Available from: https://www.fda.gov/medical-devices/medical-device-recalls/boston-scientific-corporation-recalls-emblem-s-icd-subcutaneous-implantable-cardioverter
13. Quast AFBE, Baalman SWE, Brouwer TF, et al.: A novel tool to evaluate the implant position and predict defibrillation success of the subcutaneous implantable cardioverter-defibrillator: The PRAETORIAN score. Heart Rhythm 2019; 16:403–410.
14. Knops RE, Brouwer TF, Barr CS, et al.: The learning curve associated with the introduction of the subcutaneous implantable defibrillator. Europace 2016; 18:1010–1015.
15. Biffi M, Ammendola E, Menardi E, et al.: Real-life outcome of implantable cardioverter-defibrillator and cardiac resynchronization defibrillator replacement/upgrade in a contemporary population: Observations from the multicentre DECODE registry. Europace 2019; 21:1527–1536.
16. Knops RE, Olde Nordkamp LRA, Delnoy P-PHM, et al.: Subcutaneous or Transvenous Defibrillator Therapy. New England Journal of Medicine 2020; 383:526–536.
17. Gutleben K, Nelovic V, Pujdak K, Werner M, Osmani I, Kähler J: Fracture of an S- ICD lead after two prior transvenous lead- related complications with conventional defibrillators. Pacing and Clinical Electrophysiology Blackwell Publishing Inc., 2020; 43:1491–1494.
18. Ip JE: Premature battery depletion of EMBLEM subcutaneous implantable cardioverter-

defibrillators. Journal of Cardiovascular Electrophysiology J Cardiovasc Electrophysiol, 2021; :jce.14935.
19. Burke MC, Gold MR, Knight BP, et al.: Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE study and EFFORTLESS registry. Journal of the American College of Cardiology 2015; 65:1605–1615.
20. Auricchio A, Schloss EJ, Kurita T, et al.: Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms: PainFree SST trial primary results. Heart Rhythm 2015; .
21. El-Chami MF, Burke MC, Herre JM, et al.: Outcomes of subcutaneous implantable cardioverter-defibrillator in dialysis patients: Results from the S-ICD post-approval study. Heart Rhythm 2020; 17:1566–1574.
22. Tompkins C, McLean R, Cheng A, et al.: End-stage renal disease predicts complications in pacemaker and ICD implants. Journal of Cardiovascular Electrophysiology 2011; .
23. Barakat AF, Wazni OM, Tarakji KG, et al.: Transvenous Lead Extraction in Chronic Kidney Disease and Dialysis Patients with Infected Cardiac Devices. Circulation: Arrhythmia and Electrophysiology 2018; 11.
24. Brunner MP, Cronin EM, Duarte VE, et al.: Clinical predictors of adverse patient outcomes in an experience of more than 5000 chronic endovascular pacemaker and defibrillator lead extractions. Heart Rhythm 2014; .
25. Frankel DS, Burke MC, Callans DJ, Stivland TM, Duffy E, Epstein AE: Impact of Body Mass Index on Safety and Efficacy of the Subcutaneous Implantable Cardioverter-Defibrillator. JACC: Clinical Electrophysiology 2018; .
26. Essebag V, Verma A, Healey JS, et al.: Clinically significant pocket hematoma increases long-term risk of device infection: BRUISE CONTROL INFECTION study. Journal of the American College of Cardiology 2016; 67:1300–1308.