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Impact of early complications on outcomes in patients with implantable cardioverter-defibrillator for primary prevention

Short title: Incidence and impact of early complications of ICD

Maria Soledad Ascoeta, MD,[1] Eloi Marijon, MD, PhD,[2] Pascal Defaye, MD,[3] Didier Klug, MD, PhD,[4] Frankie Beganton, MS,[5] Marie-Cécile Perier,MPH,[5] Daniel Gras, MD,[6] Vincent Algalarrondo, MD, PhD,[7] Jean-Claude Deharo, MD, PhD,[8] Christophe Leclercq, MD, PhD,[9] Laurent Fauchier, MD, PhD,[10] Dominique Babuty, MD, PhD,[10] Pierre Bordachar, MD, PhD,[11] Nicolas Sadoul, MD, PhD,[12] Serge Boveda, MD,[13] Olivier Piot, MD,[1] on behalf of the DAI-PP Investigators†

[1]Centre Cardiologique du Nord, Saint Denis, France;

[2] European Georges Pompidou Hospital and Paris Descartes University, Paris, France;

[3]CHU Michallon, Grenoble, France;

[4]CHRU Lille, Lille, France;

[5]Paris Cardiovascular Research Center, Inserm U970, Paris, France;

[6]Nouvelles Cliniques Nantaises, Nantes, France;

[7]CHU Antoine Béclère, Clamart, France;

[8]CHU La Timone, Marseille, France;

[9]CHU Pontchaillou, Rennes, France;

[10]CHU Trousseau, Tours, France;

[11]CHU Haut Lévêque, Bordeaux, France;

[12]CHU Brabois, Nancy, France

[13]Clinique Pasteur, Toulouse, France;

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Corresponding author:

Olivier Piot, MD

00 33 1 49 33 41 82 o.piot@ccncardio.com

Cardiologie 2 – Rythmologie, Centre Cardiologique du Nord, 32-36 rue des Moulins

Gémeaux 93207 Saint Denis cedex

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ABBREVIATIONS AF, atrial fibrillation; **CI** = confidence interval; **CRT** = cardiac resynchronization therapy; **DAI-PP** = Défibrillateur Automatique Implantable–Prévention Primaire; **EC** = early complication; **EF** = ejection fraction; **ICD** = implantable cardioverter-debrillator; **NYHA** = New York Heart Association; **OR** = odds ratio.

Keywords: Defibrillator; Complication; Primary prevention; Mortality; Morbidity; Sudden death.

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Abstract: BACKGROUND The life-saving benefit of implantable cardioverterdefibrillators (ICD) has been demonstrated. Their use has increased considerably in the past decade, but related complications have become a major concern.
OBJECTIVE We assessed the incidence and effect on outcomes of early (≤30 days) complications after ICD implantation for primary prevention in a large French population.
METHODS We analyzed data from 5539 patients from the multicenter French DAI-PP registry (2002–2012) who had coronary artery disease or dilated cardiomyopathy and were implanted with an ICD for primary prevention.
RESULTS Overall, early complications occurred in 707 (13.5%) patients, mainly related to lead dislodgement or hematoma (57%). Independent factors associated with occurrence of early complications were severe renal impairment (odds ratio [OR] 1.66, 95% confidence interval [CI] 1.17-2.37, P = .02), age >=75 years (OR 1.01, 95% CI 1.00-1.02, P = .03), cardiac resynchronization therapy (OR 1.58, 95% CI 1.16-2.17, P = .01), and anticoagulant therapy (OR 1.28, 95% CI 1.02-1.61, P = .03). During a mean±SD follow-up of 3.1±2.3 years, 824 (15.8%) patients experienced ≥1 late complication (>30 days), and 782 (14.9%) patients died. After adjustment, early complications remained associated with occurrence of late complications (OR 2.15, 95% CI 1.73-2.66, P <.0001) and mortality (OR 1.70, 95% CI 1.34-2.17, P = .003).
CONCLUSION Early complications are common after ICD implantation for primary prevention, occurring in 1 in 7 patients, and are associated with an increased risk of late complications and overall mortality. Further studies are needed to investigate the underlying mechanisms of such associations.

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Introduction

The beneficial effect of an implantable cardiac-defibrillator (ICD) on primary prevention of sudden cardiac death in patients with a severe left ventricular systolic dysfunction has been well demonstrated [1–5]. However, ICD implantation has the potential for complications, with a higher rate observed in daily clinical practice than is usually reported in randomized trials [6]. To date, the extent to which early complications (ECs) are associated with morbidity and mortality in daily practice has been addressed only in limited populations [7,8,9].

In this analysis, we aimed to assess the incidence and prognosis of ECs after implantation of ICDs for primary prevention in a large French population from the Défibrillateur Automatique Implantable–Prévention Primaire (DAI-PP; NCT#01992458) registry.

Methods

Population

The DAI-PP registry enrolled all patients with coronary artery disease or dilated cardiomyopathy implanted with an ICD for primary prevention between 2002 and 2012 in 12 French centers. The registry was funded by private (Association de Rythmologie Toulousaine – Clinique Pasteur) and public sources, including the French Institute of Health and Medical Research (INSERM) and the French Society of Cardiology. The overall DAI-PP registry was coordinated by the Clinique Pasteur, Toulouse and the Paris Cardiovascular Research Centre, European Georges Pompidou Hospital, Paris (See supplementary material). The DAI-PP registry complied with the principles outlined in the Declaration of Helsinki. The data file was approved and authorized by the French data protection committee (Commission Nationale Informatique et Liberté, CNIL #913203) and by the local ethics committee of each hospital.

To be included in the registry, ICD recipients had to be at least 18 years old at the time of the implant procedure. All patients with ischemic or non-ischemic cardiomyopathy who were implanted with an ICD (single, double, or triple chamber) in the setting of primary

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prevention were enrolled in the DAI-PP follow-up program. Indications for ICD were as established by the treating physicians, but to meet the 'primary prevention' requirement there had to be no history of sudden cardiac arrest or documented ventricular tachycardia/fibrillation. Ischemic cardiomyopathy was defined as the presence of myocardial dysfunction resulting from previous myocardial infarction or history of coronary artery disease with or without revascularization (angioplasty or bypass surgery at least 3 months prior to implant). All other patients were classified as having non-ischemic cardiomyopathy.

Patients who had received ICD for secondary prevention, and primary prevention patients without structural heart disease (e.g. Brugada syndrome, long QT syndrome) or with structural heart disease other than ischemic or non-ischemic cardiomyopathy (e.g. valvular heart disease, hypertrophic cardiomyopathy, non-compaction cardiomyopathy, and arrhythmogenic right ventricular dysplasia) were excluded.

Characteristics at implantation

All variables at ICD implantation were defined and categorized according to the literature or common practice. In addition to age, sex, and New York Heart Association (NYHA) functional status, we recorded the cause of the underlying heart disease (ischemic cardiopathy or dilated cardiomyopathy), level of renal function according to the Cockroft–Gault formula (categorized as creatinine clearance ≥60, 30–60, or <30 ml/min), QRS duration, and left ventricular ejection fraction (EF). Atrial fibrillation (AF) was defined as history of AF, documented on electrocardiogram or Holter monitoring. Information on non-sustained ventricular tachycardia recorded on Holter monitoring and electrophysiology testing was collected, and classified as positive or negative. Data on coexisting medical conditions were systematically collected: cancer, chronic obstructive pulmonary disease, chronic renal failure, chronic liver disease, history of transient ischemic attack, and others (including diabetes mellitus).

The type of implanted ICD device (single [VVI] or dual [DDD] chamber, associated or not with cardiac resynchronization therapy [CRT-D], without reference to manufacturing

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companies) was recorded, and device programming was left at the treating physician's discretion. Information on medications at hospital discharge included beta-blockers, amiodarone, class Ic antiarrhythmics, sotalol, digoxin, calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, diuretics, antiplatelets, and vitamin K antagonists.

Follow-up and outcomes (including cause-of-death analysis)

We calculated the incidence of ECs, and assessed patient- and device-related factors that were associated with EC occurrence. The association of ECs with outcomes, including late complications and death, was also evaluated.

ECs were defined as those that appeared during the first 30 days after device implantation, and included lead dislodgement, bleeding or hematoma, sepsis, cardiac tamponade, pneumothorax, and death. Those included peri-operative events but also any significant event, which occurred after hospital discharge within the 30 days after implantation. ICD-related fatal or non-fatal adverse events included infections, lead dislodgement or dysfunction, and inappropriate therapy due to supraventricular tachycardia, lead dysfunction, double counting or noise. Complications that occurred after the first month post-implant were defined as late complications. Follow-up information was obtained from appointments held every 4 to 6 months for device evaluation [10]. Device interrogation printouts were checked by the local investigator for appropriate and inappropriate ICD therapy.

Late complications included inappropriate shock (classified as due to supraventricular tachycardia, lead dislodgement, double counting, and noise), infection, lead dislodgement, lead dysfunction, and ICD-related specific mortality. Vital status was obtained from the hospital or general practitioner, and controlled by the National Institute of Statistics Economical Studies (INSEE). Causes of death were obtained from the investigators or the French Center on Medical Causes of Death (CépiDc–INSERM). Information on causes of death was reviewed by 2 investigators, and classified as sudden death, other cardiovascular

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death, non-cardiovascular death, ICD-related mortality or unknown (when the quality of information did not allow the investigators to appropriately identify the cause). ICD-related mortality was defined as any death due to complication related to the presence of ICD, either during the procedure or afterwards, and classified as early and late, according to the time of occurrence (< or >30 days after ICD implant).

Statistical analysis

Preparation of this report was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting of observational studies [11].

The chi-square test was used for comparison of categorical variables and Student's t-test was used for comparison of continuous variables, where appropriate; Levene's test was used to check the homogeneity of variance; equivalent non-parametric tests were used when Kolmogorov-Smirnov was in favor of absence of normal distribution. Cox regression (forward stepwise method likelihood ratio) was used to identify predictors of mortality and appropriate therapies. The analysis of ECs and mortality were examined through the use of a Cox proportional hazard multivariable regression analysis. Previously, the proportional hazard assumptions were tested. The crude associations between outcomes and different variables were first quantified by univariable Cox regression. All covariates that reached a significance level of $P<20\%$ were then included in an initial multivariable regression model. A backward stepwise selection was applied to obtain a final model that included covariates with $P<5\%$.

Predictors were presented with the corresponding odds ratio (OR) and 95% confidence interval (CI). Binary logistic regression (forward stepwise method likelihood ratio) was performed to estimate predictors of complications. Kaplan Meier curves were constructed to estimate survivals and compared, using the log-rank test.

Results with $P<0.05$ were considered statistically significant. All data were analyzed at the Paris Cardiovascular Research Centre (INSERM U970, Cardiovascular Epidemiology Unit) using SAS program v9.4 (SAS Institute Inc., Cary, North Carolina).

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Results

DAI-PP patients

Among a total of 5539 patients enrolled in DAI-PP, the status of EC occurrence (without/with EC) was known for 5220 (94 %) patients. Baseline characteristics of patients enrolled in DAI-PP are shown in Table 1. The mean age was 62.5 years and 84.9% of patients were male. A total of 3304 (60.2%) patients presented with ischemic cardiopathy and 4489 (83.7%) had an EF <30%. Approximately one third of patients fell within each of 3 categories of QRS duration (<120 ms, 120–150 ms, and >150 ms). A majority (3916, 85.6%) of patients were in NYHA class II or III, and in sinus rhythm (3589, 76%). Regarding type of device, 1258 (22.9%) were implanted with VVI, 1280 (23.3%) with DDD, and 2952 (53.8%) with CRT.

Incidence, characteristics, and associated factors of early complications

Of 5220 patients with known EC status, 707 (13.5%) presented with an EC (Table 1). The most frequent complications were bleeding-related (hematoma, 35.9%) and lead dislodgement (20.7%) (Figure 1).

Approximately 40.5% of patients with an EC were on prior anticoagulant treatment versus 34.4% of patients without EC ($P = .005$). There were no differences in prior use of antiplatelets.

Patients who had an EC had a more severe cardiac profile than those without complications (Table 1): more EC patients had a QRS >150 ms ($P = .002$), were in NYHA class III ($P = .0002$), and had renal impairment ($P < .0001$), and fewer EC patients were in sinus rhythm ($P = .004$). Of this 13.5% total EC rate, an 8.65% was due to CRT patients, 2.75% to DDD patients, and 2% to VVI patients. EC occurrence was significantly associated with the type of device (64.6% of patients with EC had a CRT device versus 52.7% of patients without EC; $P < .0001$).

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After consideration of potential confounding factors through a multivariable analysis, independent factors associated with the occurrence of EC were severe renal impairment, CRT, prior use of anticoagulant therapy, and age >=75 years (Table 2).

Impact of early complications on outcomes

Follow-up was completed for 93.6% of patients with known EC status (mean ± SD follow-up 3.1 ± 2.3 years). During follow-up, patients with an EC had earlier battery depletion than patients without EC (*P* <.0001) (Table 1). A total of 141 (19.9%) patients with an EC died versus 641 (14.2%, *P* <.0001) of patients without EC. Causes of death were significantly different between the 2 groups, with more sudden deaths and deaths from unknown cause in patients with EC (Table 1).

After multivariable analysis for mortality, ECs were independently associated with a higher risk of overall mortality. NYHA class II–IV, renal impairment, reduced ejection fraction, age ≥=75 years, ischemic cardiomyopathy, and AF were also associated with a higher risk of mortality (Table 2). Survival curves for mortality according to the occurrence of early complication are shown in Figure 2.

Data for late complications was complete for 5306 patients. Overall, 824 of 5306 (15.5%) patients presented with a late complication. Lead dysfunction or dislodgement (338/824, 41.0%) and inappropriate shocks (286/824, 34.7%) were the most common complications. We found no differences in mortality in patients with and without late complications (14.9 vs 15.3%, P=0.77).

After multivariable analysis, late complications were more frequent among patients presenting with an EC (OR 2.15, 95% CI 1.73–2.66, *P* <.0001).

Discussion

In this large, multicenter population of patients with ICD for primary prevention in France, we found an EC rate of 13.5%. To our knowledge this is the first study to present a controlled follow-up of complications in a large homogeneous population of patients undergoing primary

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prevention ICD. In this sense, we demonstrated to what extent these ECs are associated with worse outcome, including mortality, during follow-up exceeding 3 years. The negative effect of EC on outcomes has been long suspected [6], and has been evaluated in a mixed group of primary and secondary prevention patients [9], but never in such a large real-life primary prevention population.

Few authors have reported rates for EC beyond the hospitalization period. Reported rates vary from 1.8% to 11% with a median follow-up of 1 year [7,8,12–15], with most reports coming from large administrative databases, without specific access to detailed medical records. Among ICD databases, the Implantable Cardioverter-Defibrillator Registry [15] reported a 3.2% in-hospital complication rate among patients implanted with an ICD (including replacements and upgrades) for both primary and secondary prevention. In another extensive ICD registry of 104,049 patients, Dewland et al [14] reported complication rates of 3.17% in patients receiving de novo double ICDs and 2.11% in those receiving de novo single chamber ICDs (including use for both primary and secondary prevention). Recently, Dodson et al [12] reported a lower rate of in-hospital complications of 1.8% among 240,632 patients, without distinction between use for primary or secondary prevention, and including patients with replacement procedures.

There is, however, a growing sense that complication rates might be higher when evaluated comprehensively [6,15]. Most existing information on procedural complications and their repercussions was extracted from randomized trials, with an expected underestimation of real complication rates, or from large national registries that rely on administrative data. The latter usually underreport complications and comorbid illnesses, and do not reflect the actual clinical situation of implanted patients.

The EC rate of 13.5% in our study is around 4-fold higher than that found in registries that rely on administrative data[12,14,15]. Although differences in the definition of EC or patient populations might account for some of the variation across studies, our findings suggest that administrative data may indeed be suboptimal for assessing the real EC rate, and, therefore, their consequences for morbimortality. Data available in North America have relied on large

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administrative databases and claims data, which, while valuable, have some inherent limitations as opposed to direct access to patient medical records and physician-guided adjudication of outcomes, without information on temporal trends for appropriate therapies. Indeed, compared to administrative databases, each case enrolled in the DAI-PP program was "manually" checked and entered in the database, and all outcomes centrally reviewed. The fact that peri-operative complication did not included only those occurring during the index in-hospital stay may explain also the difference.

Factors associated with early complications

Previous studies have shown that older age, AF, electrical storm, and coexisting conditions are associated with a higher risk of complications following ICD implantation [9,12,15,16]. In our study, older age and severe renal impairment were associated with a higher risk of EC. The number of ICD leads is another factor that has repeatedly been associated with the risk of complications [14,17,18]. Dewland et al [14] showed in the National Cardiovascular Data Registry ICD Registry population that dual-chamber device implantation was associated with increases in periprocedural complications and in-hospital mortality compared with single-chamber defibrillators. Although the detrimental effects of dual-chamber pacing modes in patients without an indication for pacemaker therapy have been described [19], in this previous study fewer than half of patients receiving dual-chamber ICDs had such a pacing indication. Furthermore, and consistent with our finding that CRT was independently associated with EC, an OR for complications of 1.7 to 1.8 has been reported for use of a biventricular device [12,15]; both this and an elevated NYHA class were the most important predictors of complications in patients with a de novo ICD implantation. In our population, nearly 70% of patients had a QRS >120ms, and half of them had a QRS >150ms. Almost 85% were in NYHA functional class II-III. In this sense, more than half of our patients were implanted with a CRT-D, and this high rate of complex patients might partially explain our 13.5% complication rate.

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We found that prior anticoagulant treatment was associated with EC, probably related to hematoma and sepsis. These results are broadly consistent with previous literature [9], although the effect of anticoagulant therapy in our study was relatively modest (OR of 1.30). Of note, management of anticoagulation therapy was left to the physicians' discretion depending on the hemorrhagic and embolic risks of each patient, and at the time of inclusion, bridging anticoagulation was a frequent practice according to (previous) guidelines [20,21]. An increasing number of centers are now performing ICD implantation without interruption of oral anticoagulation in response to new evidence from trials [22,23]. It would be interesting to evaluate the incidence of EC and overall mortality in the same population with current perioperative anticoagulation practice.

Relation between early complications, late complications, and mortality

In our study, ECs were associated with significantly higher rates of late complications and mortality over a 3-year follow-up. Lee et al [9] also described an association between early major complications and mortality, with a hazard ratio of 3.79 in a population of 3340 patients with both primary and secondary prevention implants; this risk was maintained at 180 days.

A plausible hypothesis of the association between ECs and late complications is that the first could trigger the latter: an early hematoma may trigger a subsequent sepsis, and an early lead dislodgement could be related to a particularly difficult right ventricular anatomy resulting from a more complex underlying cardiomyopathy. Early lead dislodgement could also determine an early lead replacement with a subsequent higher risk of infection. In the same way, a more complex cardiac pathology may express itself in a higher risk of mortality.

Especially in primary prevention, optimization of the risk–benefit ratio has relied on identifying mortality-associated factors and, therefore, on improving our selection of patients. As also described in the literature, we found that renal impairment, higher NYHA class, lower EF, and older age are associated with a worse prognosis.

Our results present the relation between ECs and worse outcome in terms of mortality in patients implanted with an ICD in primary prevention. Given that ECs are an

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independent risk factor for mortality, it is evident that we should do our best to prevent them. A result of this is the constant search for new technologies that avoid endovascular access such as subcutaneous ICD's (S-ICD), which to these days show safe results along with a low complication rate. Recently, Burke et al. [24] reported a 4.5% EC complication rate and a 11.1% late complication rate in patients implanted with an S-ICD, with a 3-year estimated mortality rate of 4.2%. However, it is to say that their population differs significantly from ours, with a mean age of 50 years and an EF of 39% compared to 62 years and 25%, respectively, for our patients. On the other hand, endovascular devices are still the gold standard for defibrillation therapy and the search for improving in this area should continue. In the EC case, prevention could be achieved by a better selection of patients and by better management of patients already presenting an EC risk factor. In our study we identified 2 risk factors (anticoagulation treatment and resynchronization therapy) that predict EC. However, as they are not direct risk factors for mortality, we cannot use them for selecting patients. Nevertheless, they may be useful for identifying a subpopulation that requires more specific care to avoid ECs and to improve mortality outcomes (e.g. by enhancing renal function before implantation, or by better adjustment of anticoagulation treatment).

Study limitations

Although our data are some of the first to assess the association between EC and outcomes, we acknowledge some limitations. Our study design is retrospective, and does not capture variables such as procedure and fluoroscopy time, or physician or center procedure volume, which have also been reported as predictors of ICD complications [13].

Conclusion

In a large multicenter population of primary prevention ICD patients, we observed an EC rate of 13.5%. ECs in this patient population were associated with the occurrence of late complications and with higher mortality. Efforts are therefore needed to prevent ECs by dedicated management of patients before and after ICD implantation.

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CLINICAL PERSPECTIVES

Implantable cardiac-defibrillators (ICDs) are important for the primary (and secondary) prevention of sudden cardiac death in at-risk patients, but are associated with post-implantation complications. We report the largest analysis to date of the incidence of early complications, and their impact on patient outcomes, in a real-world ICD primary prevention population. Early complications (including bleeding/hematoma and lead dislodgement) occurred in 13.5% of patients, and were a risk factor for late complications and for mortality during follow-up. Care is therefore needed to minimize the occurrence of complications following ICD implantation, through improved selection of patients, and optimal management of those at increased risk of early complications.

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Figure 1. Types of early complications (n=707).

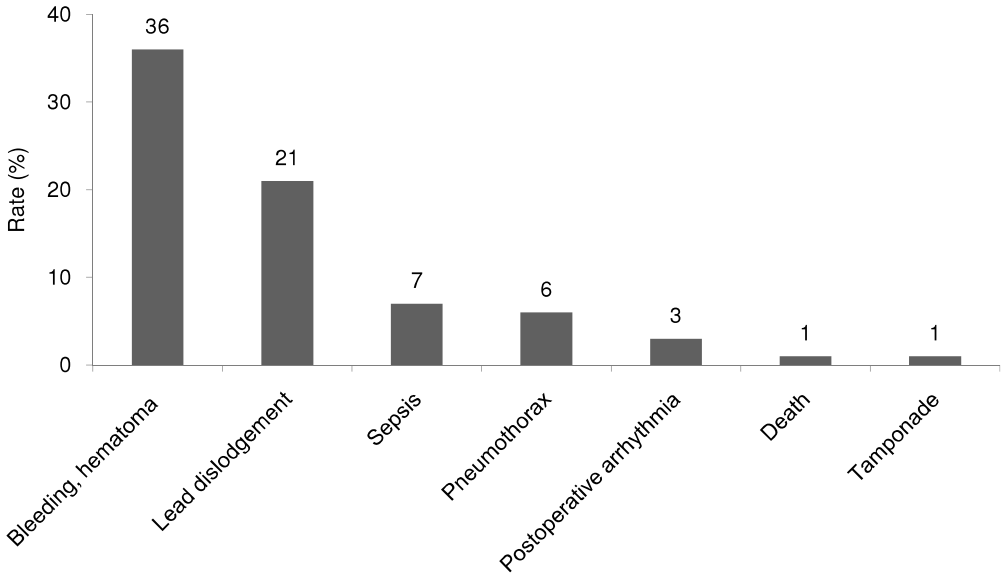

Figure 2. Survival curves for mortality according to the occurrence of early complication.

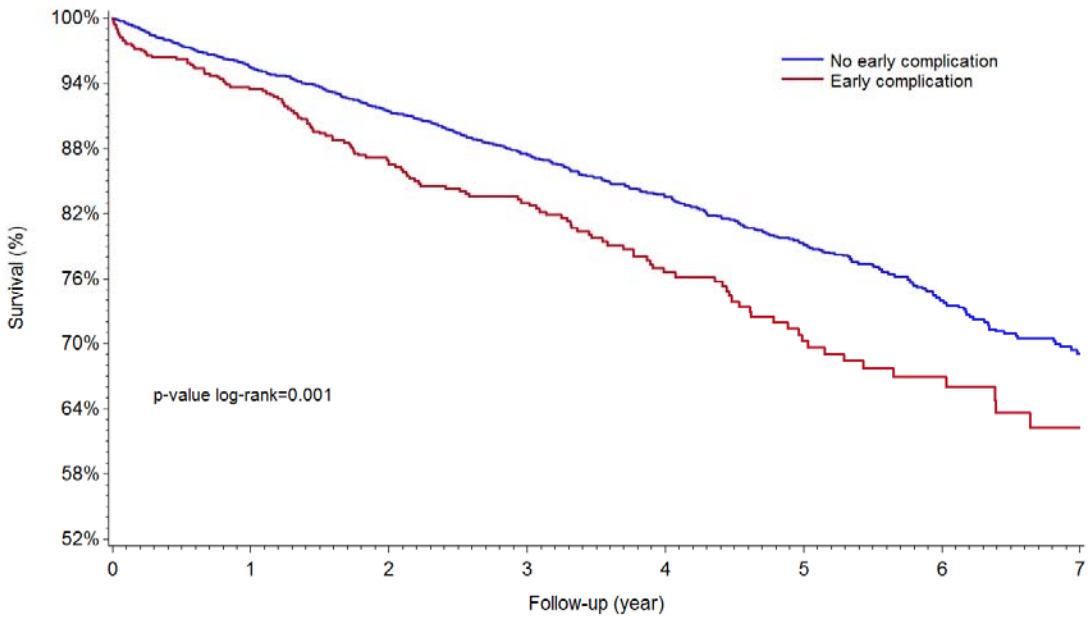

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Table 1. Characteristics and outcomes associated with early complications.

Variable	All patients N=5539	No early complication N=4513	Early complication N=707	*P*-value
Age, years (SD) [N=5215]	62.5 (11.2)	62.2 (11.2)	64.5 (10.8)	<.0001
Men, n (%)	4729 (84.9)	3826 (84.8)	597 (84.4)	.82
Cardiopathy, n (%) [N=5173]				
Ischemic	3304 (60.2)	2697 (60.2)	413 (59.4)	.69
Dilated	2181 (39.8)	1781 (39.8)	282 (40.6)	
Left ventricular ejection fraction, %, n (%) [N=5118]				
<30%	4489 (83.7)	3728 (84.0)	563 (82.7)	.49
30–45%	792 (14.8)	639 (14.4)	109 (16.0)	
>45%	81 (1.5)	70 (1.6)	9 (1.3)	
Median ejection fraction, % (IQR) [N=5118]	25 (22-30)	25.00 (22.0; 30.0)	27.00 (23.0; 30.0)	.07
QRS, n (%) [N=3734]				
<120 ms	1183 (30.5)	1000 (31.5)	138 (24.9)	.002
120–150 ms	1368 (35.3)	1125 (35.4)	197 (35.6)	
>150 ms	1322 (34.1)	1055 (33.2)	219 (39.5)	
NYHA class, n (%) [N=4392]				
I	482 (10.6)	424 (11.3)	47 (7.5)	.0002
II	1853 (40.6)	1546 (41.1)	226 (36.1)	
III	2052 (45.0)	1659 (44.1)	320 (51.1)	
IV	175 (3.8)	137 (3.6)	33 (5.3)	
Creatinine clearance, n (%) [N=3150]				
<30 ml/min	280 (8.7)	212 (7.8)	58 (13.6)	<.0001
30–60 ml/min	1001 (30.9)	836 (30.7)	146 (34.1)	
>60 ml/min	1957 (60.4)	1674 (61.5)	224 (52.3)	

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Sinus rhythm, n (%) [N=4529]	3589 (76.0)	3003 (77.2)	462 (72.1)	.004
Number of coexisting conditions [N=3945]				
0	1173 (28.0)	930 (27.7)	154 (26.2)	.37
1	2339 (55.9)	1900 (56.6)	326 (55.4)	
2	526 (12.6)	410 (12.2)	86 (14.6)	
≥3	147 (3.5)	116 (3.5)	23 (3.9)	
Type of device, n (%) [N=5203]				
CRT	2952 (53.8)	2373 (52.7)	453 (64.6)	<.0001
DDD	1280 (23.3)	1046 (23.2)	144 (20.5)	
VVI	1258 (22.9)	1083 (24.1)	104 (14.8)	
Prior treatment				
Anticoagulants (VKA)	1404 (35.28)	1126 (34.4%)	238 (40.5)	<.005
Antiplatelets	2278 (57.2)	1859 (56.8%)	351 (59.7)	.19
Outcomes				
Battery replacement, n (%) [N=4930]	1023 (19.54)	723 (17.0)	171 (25.2)	<.0001
Mean time to battery replacement, years (SD) [N=870]	3.87 (1.91)	4.1 (1.8)	2.8 (2.0)	<.0001
Transplant, n (%) [N=5132]	176 (3.24)	149 (3.4)	12 (1.7)	.023
Death, n (%) [N=5132]	826 (15.22)	641 (14.2)	141 (20.2)	<.0001
Cause of death				.006
Other cardiovascular	407 (49.27)	325 (50.7)	61 (43.3)	
Non-cardiovascular	197 (23.85)	162 (25.3)	25 (17.7)	
Sudden	64 (7.75)	46 (7.2)	16 (11.4)	
Unknown cause	144 (17.43)	99 (15.4)	34 (24.1)	

CRT = cardiac resynchronization therapy; **EF** = ejection fraction; **IQR,** interquartile range; **NYHA** = New York Heart Association; **SD** = standard deviation

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Table 2. Multivariable analysis for early complications and overall mortality.

Characteristic	Odds ratio	95% confidence interval	*P*-value
Early complication			
Severe renal impairment (creatinine clearance <30 ml/min)	1.66	1.17–2.37	.02
Cardiac resynchronization therapy	1.58	1.16–2.17	.01
Prior use of anticoagulant therapy	1.30	1.02–1.61	.03
Age >=75 years	1.01	1.00–1.02	.03
Mortality			
NYHA class II–V	1.76	1.41–2.16	<.0001
Creatinine clearance <30 ml/min	1.77	1.43–2.16	<.0001
Ejection fraction ≤30%	1.69	1.38–2.07	<.0001
Age ≥75 years	1.02	1.00–1.03	.002
Ischemic cardiomyopathy	1.29	1.05–1.57	.01
Atrial fibrillation	1.33	1.09–1.63	.006
Early complication	1.70	1.34–2.17	<.0001

NYHA = New York Heart Association

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