

# Heart failure hospitalizations and costs in ICD/CRT-D recipients following replacement or upgrade: the DECODE registry

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## Abstract

**Aims** The aim of this study is to report heart failure hospitalization (HFH) rates and associated costs within 12 months following implantable cardioverter defibrillator (ICD)/cardiac resynchronization therapy defibrillator (CRT-D) device replacement or upgrade from ICD to CRT-D.

**Methods and results** The DEtect long-term COmplications after icD rEplacement (DECODE) was a prospective, single-arm, multicentre cohort study that explored complications in ICD/CRT-D recipients. All clinical and survival data at 12 months were prospectively analysed. For each adjudicated HFH, admission and discharge dates and ICD-9-CM diagnosis and procedure codes were recorded. The reimbursement for each HFH was calculated for each diagnosis-related group code. Between 2013 and 2015, 983 patients (mean age 71 years, male 76%, mean left ventricular ejection fraction 35%, and New York Heart Association Class I/II 75.6%) were enrolled. Patients underwent device replacement (900; 91.6%, 446 ICD/454 CRT-D) or ICD upgrade to CRT-D (83; 8.4%). Post-replacement hospitalizations occurred in 220 patients, with the primary discharge diagnosis identifying cardiovascular causes in 175 patients (80%). Fifty-five (5.6%) patients experienced at least one HFH. Overall, 91 HFH events occurred (9.6% event rate, 95% confidence interval: 7.7–11.7) in 70 patients; 66 (6.7%) patients died, 40 (60.6%) of cardiovascular causes. The HFH rate was significantly higher following upgrades, and the occurrence of HFH was associated with an 11-fold increased mortality risk (95% confidence interval: 5.9–20.5,  $P < 0.0001$ ). Medical diagnosis-related group accounted for 91.2% of HFH; the mean cost per HFH was €5662 ± 9497, and the mean cost per patient was €9369 ± 12 687. On multivariate analysis, predictors of HFH were atrial fibrillation, chronic kidney disease, and all-cause hospitalization within 30 days prior to the procedure.

**Conclusions** In the DECODE registry, HFH and mortality rates in the year following ICD/CRT-D replacement or upgrade were low. In this particular subset, underlying cardiac disease was the main driver of HFH, mortality, and higher healthcare expenditures.

**Keywords** Cardiac resynchronization therapy; Costs; Device replacement; Heart failure hospitalization; Implantable cardioverter defibrillator

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## Background

Heart failure (HF) is a major public health problem in Europe and North America<sup>1,2</sup> and one of the leading causes of hospital admission.<sup>3</sup> HF patients constitute a heterogeneous population that is consistently associated with high management costs, most of which are driven by HF hospitalizations (HFHs), regardless of the case mix.<sup>2,3</sup> Non-pharmacological interventions, that is, the use of cardiac implantable electronic devices for the prevention of sudden cardiac death and for the electrical manipulation of the failing heart, are established therapeutic options in patients with HF with reduced ejection fraction (HFrEF).<sup>4–6</sup> While the healthcare expenditure associated with HFH is high in recipients of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-Ds), the event rate of HFH and its associated costs after device replacement or upgrade are unknown.

## Aims

The aims of this study were to report HFH rates, and associated costs from an Italian healthcare payer perspective, within 12 months following ICD/CRT-D device replacement or upgrade from ICD to CRT-D; to identify potential predictors of HFH; and to investigate the association of HFH with short-term mortality in this particular population of cardiac implantable electronic device recipients.

## Methods

### Study design and patient population

The DETect long-term COmplications after icD rEplacement (DECODE) trial was a prospective, single-arm, multicentre cohort study aimed at providing an estimate of medium-term to long-term complications in a large population of ICD/CRT-D recipients undergoing device replacement or upgrade from ICD to CRT-D from 2013 to 2015.<sup>7</sup> Patient characteristics collected on replacement/upgrade were age, gender, body mass index, estimated glomerular filtration rate, left ventricular ejection fraction, HF status, medical history, co-morbidities, medications, and procedural details. For the purpose of this analysis, all clinical and survival data on these patients at 12 months were prospectively analysed. The primary endpoint was HFH. All hospital admissions occurring within 12 months following device replacement/upgrade were identified, and the medical records of the patients involved were reviewed by an event adjudication committee. The study complied with the Declaration of Helsinki, the research protocol was approved by the local ethics committees, and written

informed consent was obtained from the all the subjects (or their guardians).

### Assessment of the type of heart failure hospitalization and associated costs

For each adjudicated HFH, the admission and discharge date were recorded, and ICD-9-CM diagnosis and procedure codes were obtained. A diagnosis-related group (DRG) code (Version v24, 1 October 2006) for each hospitalization was determined from all diagnosis and procedure codes by means of the Grouper software 'Applicazioni di codifica 3 M' (Version 6.4.1, April 2011, 3M Health Information Systems, Italy). Finally, the estimated reimbursement for each hospitalization was obtained for the DRG according to the 2012 Italian national reimbursement rates (National Ministerial Tariffs, Ministerial Decree of 18 October 2012).

### Statistical analysis

Continuous data are expressed as mean  $\pm$  standard deviation or median values with inter-quartile range, as appropriate, for all the variables. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed by means of Cox regression models, in which baseline parameters were taken as fixed covariates and endpoint events were taken as time-dependent covariates. The Kaplan–Meier method was used to analyse estimates of time to death over 12 month follow-up according to HFH events. A two-sided *P*-value  $<0.05$  was considered statistically significant. All statistical analyses were performed by means of STATISTICA software, Version 7.1 (StatSoft, Inc., Tulsa, OK, USA).

## Results

### Patient demographics

The patients' main characteristics are reported in *Table 1*. Between 2013 and 2015, 983 consecutive patients (mean age 71 years, mean left ventricular ejection fraction 35%, male 76%, and secondary prevention ICD 35.4%) were enrolled in the DECODE registry. Most patients were in New York Heart Association Class I/II (75.6%) and had HF due to ischaemic causes (56%). Hypertension, atrial fibrillation (AF), and diabetes were common medical conditions in the study cohort. Overall, the patients were adequately treated with evidence-based pharmacotherapy for HFrEF, except for sacubitril/valsartan,<sup>8</sup> which became available after completion of the DECODE follow-up period. Patients underwent device replacement of the same type in 900 cases (91.6%),

**Table 1** Demographics and baseline characteristics of the study population

Patients' characteristics	n = 983
Age (years)	71 (63–77)
LVEF (%)	35 (30–45)
Body mass index (kg/m <sup>2</sup> )	26.3 (24–29.4)
eGFR (mL/min)	63.3 (44.5–84)
Male gender, n (%)	750 (76.3)
Secondary prevention ICD, n (%)	348 (35.4)
NYHA I, n (%)	191 (19.4)
NYHA II, n (%)	553 (56.3)
NYHA III, n (%)	225 (22.9)
NYHA IV, n (%)	14 (1.4)
History of atrial fibrillation, n (%)	372 (37.8)
Atrioventricular node ablation, n (%)	41 (4.2)
Ischaemic cardiomyopathy, n (%)	537 (54.6)
Myocardial revascularization within 6 months prior to the procedure, n (%)	95 (9.7)
Diabetes, n (%)	282 (28.7)
Hypertension, n (%)	608 (61.9)
Chronic kidney disease, n (%)	249 (25.3)
Ictus/TIA/SEE, n (%)	84 (8.5)
History of cancer, n (%)	60 (6.1)
COPD, n (%)	189 (19.2)
Current smoker, n (%)	62 (6.3)
All-cause hospitalization within 30 days prior to the procedure, n (%)	73 (7.4)
ACE inhibitors, n (%)	555 (56.5)
Ivabradine, n (%)	59 (5)
Angiotensin receptor blockers, n (%)	186 (18.9)
Beta-blockers, n (%)	839 (85.4)
Statins, n (%)	515 (52.4)
Loop diuretics, n (%)	701 (71.3)
Mineralocorticoid receptor antagonists, n (%)	448 (45.6)
Amiodarone, n (%)	218 (22.2)
Oral antidiabetics, n (%)	164 (16.7)
Insulin, n (%)	99 (10.1)
Warfarin, n (%)	408 (41.5)
Direct oral anticoagulants, n (%)	3 (0.3)
Single antiplatelet, n (%)	402 (40.9)
Dual antiplatelet, n (%)	35 (3.6)
Warfarin + antiplatelet, n (%)	113 (11.5)
Replacement procedure, n (%)	804 (81.8)
System upgrade, n (%)	179 (1.2)
Device replaced: single-chamber, n (%)	257 (26.1)
Device replaced: dual-chamber, n (%)	261 (26.6)
Device replaced: VDD, n (%)	5 (0.5)
Device replaced: CRT-D, n (%)	460 (46.8)
Appropriate shock therapy prior to ICD replacement, n (%)	348 (35.4)

ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SEE, systemic embolic events; TIA, transient ischaemic attack.

including 446 ICDs and 454 CRT-Ds, and with an upgrade from ICD to CRT-D in 83 cases (8.4%).

## Post-replacement heart failure hospitalizations and mortality

Overall, 220 patients were hospitalized at least once following device replacement. Of those hospitalizations, the primary

discharge diagnosis was cardiovascular in 175 (80%) and non-cardiovascular in 45 (20%), as detailed in Supporting Information, *Table S1*. Specifically, HF and procedure-related complications were the two most frequent cardiovascular causes of post-replacement hospitalization [in 70 (32%) and 49 (22%) cases, respectively]. Over a mean follow-up of  $353 \pm 49$  days, 55 (5.6%) patients experienced at least one HFH. Overall, 91 HFH were reported (9.6% event rate, 95% CI: 7.7–11.7), in 70 patients, with a median time to first HFH of 150 (81.5–231.5) days. Most patients ( $n = 35$ , 64%) experienced only one HFH, with 19 (34.5%) behaving as frequent flyers and 1 patient experiencing six events. The HFH rate (*Figure 1*) was significantly higher following upgrade procedures than after replacement [ $n = 10$  (12%) undergoing clinical upgrade vs.  $n = 45$  (5%) undergoing replacement,  $P = 0.02$ ].

On univariate analysis, a previous history of AF, chronic kidney disease (CKD), left ventricular ejection fraction  $\leq 35\%$ , New York Heart Association Class III/IV vs. I/II, and all-cause hospitalization within 30 days prior to the replacement or upgrade procedure were predictors of HFH over 12 months of follow-up. On multivariate analysis adjusted for baseline confounders, AF (HR 1.77, 95% CI 1.02–3.06,  $P = 0.04$ ), CKD (HR 2.36, 95% CI 1.02–3.06,  $P = 0.002$ ), and all-cause hospitalization within 30 days prior to the procedure (HR 5.61, 95% CI 3.11–10.12,  $P < 0.0001$ ) remained significant and independent HFH predictors (Supporting Information, *Table S2*). The time to HFH was significantly shorter in patients who had a history of AF (Supporting Information, *Figure S1A*) (log-rank  $P = 0.0032$ ), CKD (Supporting Information, *Figure S1B*) (log-rank  $P = 0.0001$ ), and hospitalization within 30 days prior to the procedure (Supporting Information, *Figure S1C*) (log-rank  $P < 0.0001$ ). The mortality rate was 6.7% (66 patients), of whom 40 (60.6%) died of cardiovascular causes and 26 of non-cardiovascular causes. The mean time to death was  $209 \pm 98$  days, which was significantly shorter in patients with at least one HFH than in those without (*Figure 2*). The occurrence of HFH was associated with an 11-fold increased mortality risk (95% CI: 5.9–20.5,  $P < 0.0001$ ).

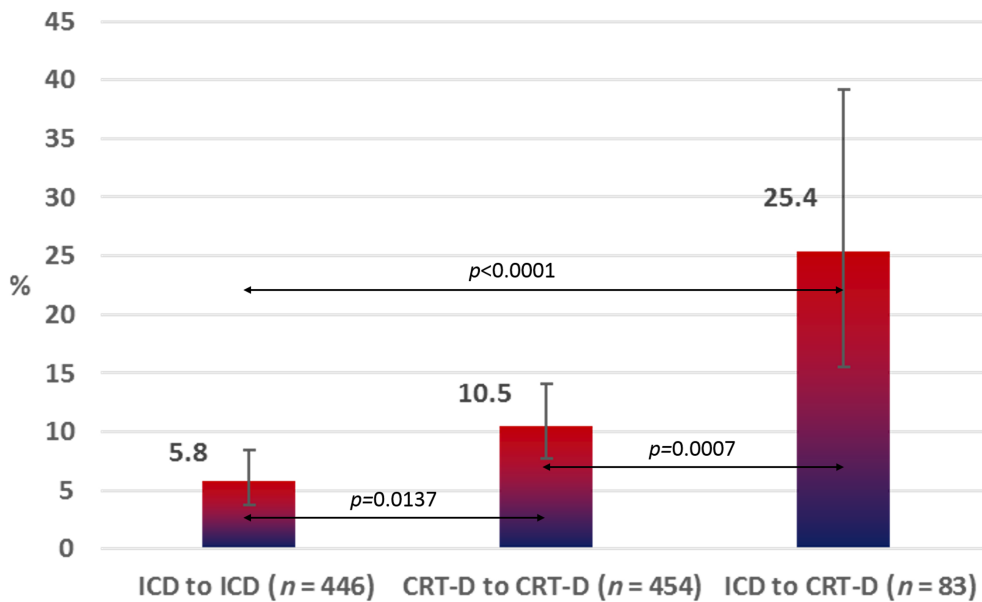
## Heart failure hospitalization cost analysis

Surgical DRGs accounted for 8.8% of HFH and medical DRGs for 91.2%; the cumulative HFH costs incurred over the 12 month follow-up were €515 305. The mean cost per HFH was €5662  $\pm$  9497, while the mean cost per patient was €9369  $\pm$  12 687.

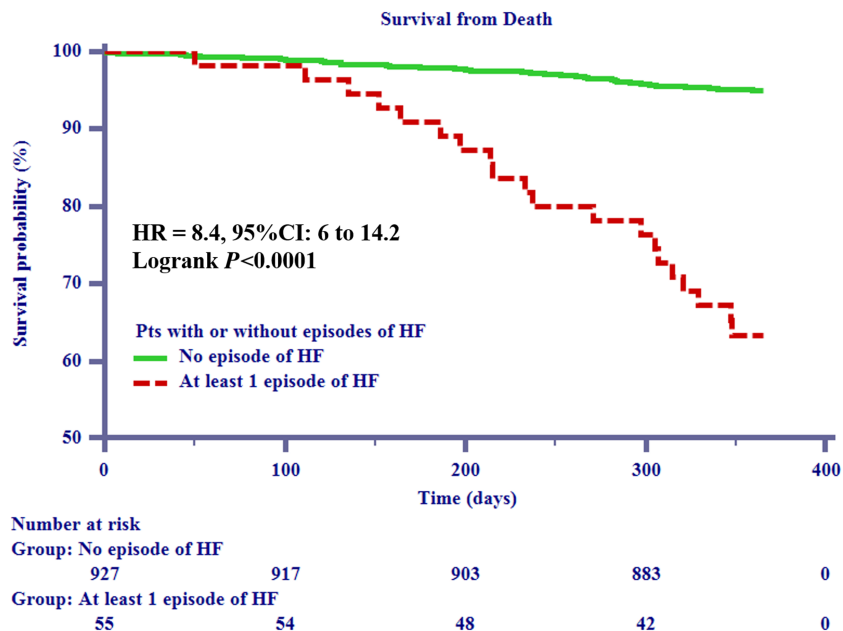
## Discussion

In this first analysis of HFH and its associated costs in a cohort of patients undergoing ICD/CRT-D replacement, the

**Figure 1** Comparison of heart failure hospitalization rate according to procedure type: replacement [implantable cardioverter defibrillator (ICD) to ICD or cardiac resynchronization therapy defibrillator (CRT-D) to CRT-D] and upgrade (ICD to CRT-D).



**Figure 2** Kaplan–Meier estimates of time to death over 12 month follow-up in patients who experienced at least one heart failure (HF) hospitalization compared with those who did not. CI, confidence interval; HR, hazard ratio.



progression of the underlying cardiac disease proved to be the main driver of HF-related hospitalization, mortality, and higher healthcare expenditures in ICD/CRT-D recipients following device replacement or upgrade from ICD to CRT-D. Indeed, both ejection fraction <35% and upgrade to CRT-D—which pinpoint an underlying HF status—were associated

with hospitalization in the 30 days prior to the device procedure. In this regard, our results showed that patients with previous hospitalization had a six-fold higher probability of HFH than those without previous hospitalization and thus identified a frail population that is not easy to monitor. Additionally, HFH-related costs obtained by calculating the DRG

code based on the actual procedures performed in individual patients (€5662) were markedly higher than those commonly reported and adopted in cost analyses, namely, €3052 as per DRG127 (<http://www.gazzettaufficiale.it/eli/gu/2013/01/28/23/sg/pdf>). This highlights the difference between clinical patients with HF together with other co-morbidities and estimates of a theoretical base case.

Event rates in the DECODE registry were lower than those reported in contemporary HFREF populations.<sup>8,9</sup> Overall, the HFH and mortality rates can be deemed to reflect a low-risk subset of stable patients optimally treated for HF with both pharmacological and device therapies who underwent elective generator replacement. Only 5.6% of patients, who displayed a baseline HF prevalence of 71%, underwent HFH in our population. This can be viewed as a marker of substantially good HF management at the time of study enrolment (despite the unavailability of sacubitril/valsartan). Conversely, on adopting upgrade to CRT-D as a proxy for more severe disease and higher risk, this condition markedly increased the HFH rate and, in turn, the mortality risk. Nonetheless, specific management programmes should be adopted in the subset of patients hosting markers of more advanced HF stages.<sup>10</sup>

A history of AF, CKD, and previous hospitalization were predictive of HFH during follow-up. AF heavily impacts healthcare expenditures at different levels: the general population (e.g. stroke prevention and anticoagulation monitoring), cardiovascular patients when AF is a secondary diagnosis during admission (hospitalizations and management of AF-related complications), and the HF population, in which AF triggers clinical deterioration and HFH through several pathophysiological mechanisms (e.g. loss of CRT, worsening/onset of mitral regurgitation, and side effects of drug therapy).<sup>11</sup> In this perspective, it seems that AF should be carefully evaluated and treated according to the individual patient's circumstances when planning device replacement/upgrade. Doing so may improve the clinical outcome and possibly impact the cost of disease management<sup>12–14</sup> (Supporting Information, *Figures S2 and S3*). The economic burden of CKD is substantial. Indeed, as shown by several studies, CKD patients generate higher costs than patients without CKD who are matched for age and co-morbidity.<sup>15</sup> Moreover, those with CKD, even when they are not on dialysis at the baseline, generate high healthcare costs, which increase as the severity of CKD increases.<sup>16,17</sup> Therefore, real-time monitoring of renal function in HF patients could contribute substantially to reducing costs in this clinical setting. With regard to the crucial role of renal monitoring, dedicated advanced HF units have been developed in order to target the specific needs of the many patients with advanced HF.<sup>18</sup> The economic burden of HF is further compounded by a particularly high readmission rate, as nearly 25% of HF patients are readmitted within 30 days.<sup>19</sup>

Regardless of the disease stage, HFH event rates and, hence, the related costs may be curbed by the systematic

implementation of remote monitoring.<sup>20</sup> Moreover, in eligible patients with HFREF, replacing an angiotensin-converting enzyme inhibitor with an angiotensin receptor–neprilysin inhibitor should be considered in order to further reduce HF mortality and morbidity<sup>5</sup>; this approach is also cost-effective,<sup>21</sup> displaying a more effective and cost-saving profile even when tested against an ICD-oriented strategy.<sup>22</sup> Regrettably, sacubitril/valsartan therapy was not available during the enrolment phase and follow-up period of the DECODE registry, and the potential of this innovative treatment to positively impact outcomes in this subset of patients, although very plausible, remains to be explored. It must be noted, however, that new HFH accounted for no more than one-third of hospitalizations in our population, highlighting the role of co-morbidities in determining clinical events (Supporting Information, *Table S1*) and underlining the importance of comprehensive patient evaluation in order to optimize disease management.

## Conclusions

In the DECODE registry, HFHs and mortality rates in the year following ICD/CRT-D replacement or upgrade were low. Underlying cardiac disease is the main driver of HFH, mortality, and higher healthcare expenditures, even in patients undergoing device replacement or upgrade who have a low HFH rate. Careful, scheduled monitoring of the underlying cardiac disease by an ambulatory HF unit might impact HFH risk and its associated costs in these patients. Comprehensive patient evaluation, which could be facilitated by remote monitoring/telemedicine programmes,<sup>23,24</sup> is mandatory in order to slow disease progression and specifically target associated co-morbidities. Further investigations, including both clinical and economic analyses, are warranted in order to better inform decision making at the time of ICD replacement.<sup>25</sup>

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## Conflict of interest

The authors declare no conflict of interest.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1:** Specifics of causes of hospitalization categorized according to cardiovascular and non-cardiovascular.

**Table S2:** Univariate and multivariate predictors of HF hospitalizations over 12-month follow-up.

**Figure S1:** (A–C) Kaplan–Meier estimates of time to HF hospitalization over 12-month follow-up in patients stratified by:

**Figure S2:** History of atrial fibrillation and HF events after ICD/CRT-D replacement/upgrade:

**Figure S3:** History of atrial fibrillation and Mortality after ICD/CRT-D replacement/upgrade:

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