

Utilization and in-hospital complications of cardiac resynchronization therapy: trends in the United States from 2003 to 2013

Seyed Mohammadreza Hosseini^{1,2†}, Kasra Moazzami^{1,2†}, Guy Rozen^{1,2},
Jeena Vaid^{1,2}, Ahmed Saleh^{1,2}, E. Kevin Heist^{1,2}, Mark Vangel³, and
Jeremy N. Ruskin^{1,2*}

¹Cardiac Arrhythmia Service, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA; ²Department of Medicine, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA; and ³Department of Biostatistics, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

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Aims

Cardiac resynchronization therapy (CRT) device implantation has been shown to reduce morbidity and mortality in selected patients with heart failure. We sought to investigate the utilization and in-hospital complications of cardiac resynchronization therapy defibrillator (CRT-D) and pacemaker (CRT-P) implantations in the United States from 2003 to 2013.

Methods and results

Patients receiving CRT-D or CRT-P were identified in the National Inpatient Sample database (NIS), using the International Classification of Diseases-Ninth Revision-Clinical Modification procedure codes. Annual implantation rates, patient demographics, co-morbidities, in-hospital complications, and length of stay were analysed. From 2003 to 2013, an estimated total of 439 010 (95% CI: 406 723–471 296) inpatient CRT implantations were performed in the U.S. The median age of patients was 72 and 71% were male. Overall, 6.1% had at least one complication. During the study period, comorbidity index and overall complication rate increased ($P=0.002$ and $P=0.01$, respectively). Mortality and length of stay showed no significant trend. Predictors of complications included: age 65 and older, female sex (OR: 1.19; 95% CI: 1.12–1.27), Deyo–Charlson Comorbidity Index, and elective admission (OR: 0.61; 95% CI: 0.57–0.66).

Conclusion

From 2003 to 2013, the severity of comorbid conditions increased and a rising trend was observed in the rate of peri-procedural complications among patients undergoing CRT in the United States. In-hospital mortality and length of stay showed no uniform trend.

Keywords

Cardiac resynchronization therapy • Complication • Defibrillator • Pacemaker

Introduction

Cardiac resynchronization therapy (CRT) has been shown to reduce morbidity and mortality in selected patients with heart failure.^{1–3} The long-term clinical benefits of both CRT with (CRT-D) and without (CRT-P) a defibrillator have been demonstrated in several randomized clinical trials.^{4,5} These positive findings have resulted in more widespread use of CRT over the past decade.⁶

While the benefits of CRT have been confirmed by large clinical trials and population-based studies, data regarding peri-procedural

complication rates of CRT are scarce.^{1–5} Moreover, most of the existing evidence of procedure-related adverse events and the safety and effectiveness of CRT stems from clinical trials. While these studies provide robust data on efficacy, their selected patient populations and clinical settings limit their generalizability to real-world practice. It has been shown that, in terms of the clinical characteristics and associated comorbidities of patients with heart failure, significant differences exist between clinical practice and published trials.⁷ As a result, real-world data regarding complications of CRT are missing.

* Corresponding author. Tel: 617 726 8514, Fax: 617 724 6747, Email: jruskin@mgh.harvard.edu

† The first two authors contributed equally to this work.

We therefore sought to collect data on the baseline characteristics, comorbidity index, in-hospital complications, mortality, and length of stay for patients undergoing CRT device implantation during the period from 2003 to 2013 on a nationwide scale.

Methods

Data source

The data were obtained from the National Inpatient Sample and the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), and Agency for Healthcare Research and Quality (AHRQ) from 2003 to 2013.^{8,9} The NIS is the largest all-payer inpatient database of hospital discharge records in the United States. It represents approximately 20% of all discharges from a broad spectrum of U.S. hospitals. National estimates can be calculated using sampling weights provided by the NIS. The provided discharge sample weights were calculated within each sampling stratum as the ratio of discharges in the universe to discharges in the sample. Detailed information on the implementation of sampling weights are provided in the Supplementary material online.

Study design

The International Classification of Diseases- 9th Revision-Clinical Modification (ICD-9-CM) was used to identify patients age 18 years or older with a primary procedure code of CRT-P (code 00.50) or CRT-D (code 00.51) device implantation. Data regarding age, sex, race, primary and secondary procedures, and length of stay were collected using discharge records.

Associated comorbidities were identified by measures from the Agency for Healthcare Research and Quality (AHRQ). The severity of comorbidities was calculated using the Deyo modification of the Charlson Comorbidity Index (CCI), which includes 17 comorbid conditions with differential weights and a total score ranging from 0 to 33. Higher scores correspond to greater severity of comorbid diseases.¹⁰

Rates of acute in-hospital periprocedural complications were determined using the corresponding ICD-9-CM diagnosis. These included cardiac complications; pericardial complications; post-operative haemorrhage/haematoma; vascular injury; vascular injury requiring surgical repair; pulmonary complications (pneumothorax, haemothorax, chest tube placement, and other iatrogenic complications); neurological complications (stroke and transient ischaemic attack); post-operative infectious complications; and in-hospital death. ICD-9-CM codes used in this study are provided in the Supplementary material online.

Statistical analysis

For all analyses, we used survey estimation (svyset and svy) and followed the recommendations from AHRQ for analysis of survey data to account for the complex survey design of the NIS database. For calculation of national estimates and correct variances, trend weight files (called 'TRENDWWT¹¹') provided by AHRQ were used as sampling weights (pweight). For categorical variables, the χ^2 test was used for comparisons between patients receiving CRT-D and CRT-P. For continuous variables, the Wilcoxon signed rank test was used when appropriate. Trends for continuous variables were tested using the non-parametric test for trend by Cuzick.¹² Two level mixed-effects multivariable logistic regression was used to identify independent predictors of post-procedural complications. Candidate variables included those on a patient and hospital level, with patient level factors clustered within hospital level factors, as well as the comorbidity index (Deyo-CCI) and year, with a term to adjust for the interaction effect between weekend admission and elective admission. All

analyses were performed using Stata/IC 12.1 (College Station, TX: StataCorp LP.). *P*-value <0.05 was considered statistically significant.

Results

Baseline clinical characteristics

Baseline clinical characteristics and associated comorbidities of patients who underwent CRT-D or CRT-P implantation are listed in *Table 1*. A total of 92 480 unweighted observations were analysed from 2003 to 2013. After weighting the observations, it represents an estimated total of 376 045 (95% CI: 348 190–403 890) CRT-D and 62 965 (57 012–68 917) CRT-P implantations on an inpatient basis in the United States. No consistent trend was observed for the annual volume of CRT-D or CRT-P device implantations.

The median age of CRT recipients was 72 years (IQR: 63–79) and the majority of patients (71%) were male (*Table 1*). The proportion of females receiving CRT devices increased from 26.1% in 2003 to 32% in 2013 ($P = 0.002$).

Patients receiving CRT-D were younger than those receiving CRT-P (69.34 ± 0.11 vs. 75.03 ± 0.16 , respectively). The proportion of patients older than 80 who received CRT-P was more than twice that of recipients of CRT-D (*Table 1*). While the mean age of patients remained unchanged for recipients of CRT-D (68.8 ± 0.3 years in 2003 vs. 69.7 ± 0.2 years in 2013, $P = 0.54$), patients receiving CRT-P showed an increase in mean age (from 72.4 ± 0.4 years in 2003 to 76.26 ± 0.2 years in 2013, $P = 0.004$).

Overall, the most common comorbidity among all CRT recipients was a history of ischaemic heart disease (66.5%), followed by hypertension (54.1%), diabetes mellitus (27.9%), chronic pulmonary disease (20.8%), chronic kidney disease (17%), and peripheral vascular disease (8.2%) (*Table 1*). The severity of comorbid diseases, as indicated by Deyo-CCI, showed a steady increase in both groups over the study period (*Table 2*). The percentage of patients receiving CRT with a Deyo-CCI of two or more increased from 55.9% in 2003 to 70.2% in 2013 ($P = 0.002$). Patients with CRT-D had higher rates of ischaemic heart disease, diabetes mellitus, peripheral vascular diseases, and obesity compared with CRT-P recipients (*Table 1*).

In-hospital complications, length of stay, and mortality

As shown in *Figure 1*, of all CRT procedures completed from 2003 to 2013, 6.1% had at least one complication (6.04% and 6.54% for CRT-D and CRT-P implants, respectively). Patients in older age groups had significantly higher rates of complications than those in younger groups (*Figure 2*). Overall, in patients over 80 years of age, 7.1% had at least one complication. The rate of at least one complication increased in the overall population during the study ($P = 0.01$). While cardiac complications decreased among all CRT recipients ($P = 0.007$), they were offset by increasing trends in the rates of haemorrhage/haematoma ($P = 0.02$), pericardial complications ($P = 0.005$), and post-operative infection ($P = 0.01$).

Trends in the rates of complication for CRT-D and CRT-P groups are reported in *Tables 2* and *3* of the Supplementary material online, respectively. Over the study period, the overall rate of at least one complication in recipients of CRT-D devices increased from 5.86 to 6.95% ($P = 0.01$), and from 5.46 to 7.11% ($P = 0.01$) in CRT-P

Table 1 Comparison of baseline characteristics of CRT-D and CRT-P implantations 2003–2013

Demographic variable	All CRT	CRT-D	CRT-P	P-value
Total number ^a	92 480	13 293	79 187	
Weighted total number ^b	439 010	376 045	62 965	
Age (%)				<0.001
18–49	5.51	5.90	3.23	
50–64	22.44	23.98	13.26	
65–79	49.57	50.75	42.51	
>80	22.48	19.37	41.00	
Mean ± SE	70.15 ± 0.11	69.34 ± 0.11	75.03 ± 0.16	
Sex (%)				<0.001
Male	70.98	73.06	58.52	
Female	29.02	26.94	41.48	
Comorbidities (%)				
Ischaemic heart disease	66.54	68.83	52.87	<0.001
History of hypertension	54.10	54.00	54.71	0.2
History of diabetes mellitus	27.95	28.62	23.86	<0.001
History of chronic pulmonary disease	20.79	20.82	20.58	0.5
History of chronic kidney disease	17.04	17.01	17.22	0.6
History of peripheral vascular disease	8.24	8.40	7.30	<0.001
Obesity	7.59	7.79	6.34	<0.001

The percentage of patients over 80 years of age who underwent CRT-P implantation was twice that of those who received CRT-D devices.

^aRepresents the number of observations in the NIS dataset.

^bRepresents total national estimates after applying sampling weights.

Table 2 Temporal trends in complication rates, mortality, and length of stay for all CRT implantations 2003–2013

	Overall	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	P-value
Total CRT (n)	92 480	5550	8699	9820	11 512	9931	9610	9869	8201	7893	6222	5173	0.4
Weighted total CRT (n)	439 010	25 767	40 966	46 956	53 766	47 151	44 900	47 303	39 311	35 915	31 110	25 865	0.4
≥1 complication	6.11	5.76	5.58	4.93	4.49	5.54	6.34	6.75	6.75	7.45	7.34	6.98	0.01
Haemorrhage or haematoma	1.41	1.43	1.15	0.94	0.78	1.02	1.38	1.53	1.70	2.21	2.03	2.22	0.01
Vascular injury	0.32	0.50	0.43	0.28	0.34	0.32	0.28	0.35	0.33	0.23	0.10	0.33	0.07
Vascular injury requiring surgery	0.12	0.17	0.15	0.07	0.09	0.10	0.18	0.08	0.17	0.16	0.14	0.12	0.8
Cardiac	0.87	1.04	0.96	0.96	0.91	0.96	0.89	0.74	0.79	0.67	0.72	0.85	0.007
Pericardial	0.65	0.40	0.41	0.37	0.39	0.54	0.75	0.88	0.93	0.75	1.00	1.01	0.005
Pulmonary	1.48	1.42	1.45	1.52	1.34	1.31	1.66	1.47	1.61	1.54	1.54	1.49	0.1
Neurological	0.24	0.16	0.32	0.14	0.25	0.22	0.26	0.32	0.19	0.24	0.34	0.25	0.2
Infection	1.17	0.69	0.67	0.52	0.90	1.08	1.18	1.67	1.59	1.94	1.85	0.93	0.01
Mortality	0.76	0.98	1.00	0.73	0.81	0.70	0.61	0.77	0.63	0.84	0.53	0.77	0.1
Length of stay(days)	2 (1–7)±0.06	3 (1–7)±.18	3 (1–7)	2 (1–7)	2 (1–6)	2 (1–6)	2 (1–6)	3 (1–7)	3 (1–7)	3 (1–7)	3 (1–7)	3 (1–7)	0.9
Deyo-CCI	2.27 ±0.01 (0.01)	1.85 ±0.03 (0.03)	1.92 ±0.02 (0.02)	1.96 ±0.02 (0.02)	2.07 ±0.03 (0.03)	2.26 ±0.03 (0.03)	2.27 ±0.03 (0.03)	2.42 ±0.03 (0.03)	2.49 ±0.04 (0.04)	2.61 ±0.04 (0.04)	2.66 ±0.03 (0.03)	2.70 ±0.03 (0.03)	0.002

Values are n, %, mean (SEM), or median (25th, 75th percentile) (due to the skewed distribution).

P-value for trend using the non-parametric test for trend by Cuzick. P < 0.05 considered significant.

recipients. In the CRT-D group, this trend was driven by increasing trends in pericardial complications (P = 0.008), vascular complications (P = 0.02), and post-operative infections (P = 0.01). In contrast, the increase in the rate of complications for CRT-P recipients appeared to

be driven only by an increase in vascular complications (P = 0.01), since no uniform trend was observed for any other complication. The most common adverse outcomes for CRT-P implants were pulmonary complications, while in the CRT-D group, vascular

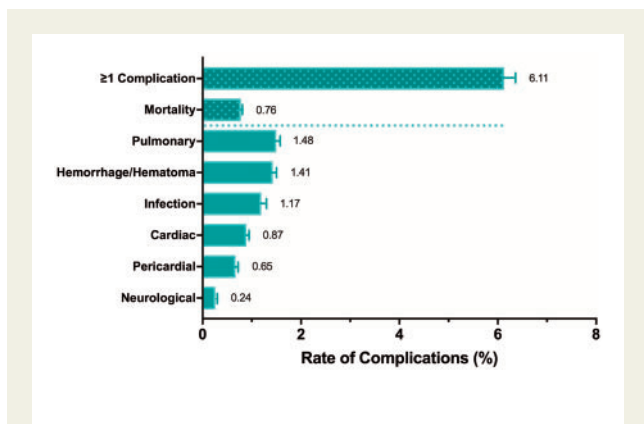


Figure 1 Types and frequencies of complications following CRT implantation. Pulmonary complications were the most common adverse events in CRT recipients.

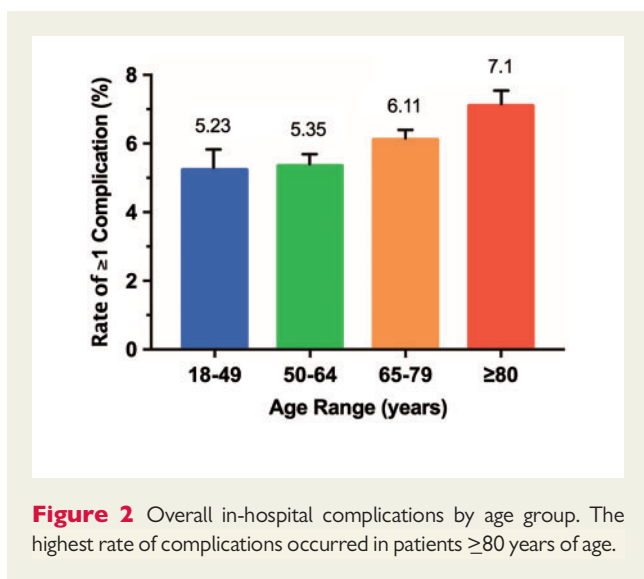


Figure 2 Overall in-hospital complications by age group. The highest rate of complications occurred in patients ≥80 years of age.

complications were most common. Among CRT-D recipients, the rate of cardiac complications decreased over time ($P = 0.02$).

The median (IQR) length of stay (LOS) for all CRT recipients was 2 (1–7), similar to the CRT-D group’s LOS. In the CRT-P group, median (IQR) LOS was 3 (1–7). The total in-hospital mortality rate was 0.76% (0.7 and 1.08% for CRT-D and CRT-P implants, respectively). No significant trend was observed in mortality or length of stay for either group (see Supplementary material online).

Predictors of in-hospital complications

Results of the multivariable logistic regression model are shown in Table 3. Age was a significant predictor of complications. There was a stepwise increase in the odds of in-hospital complication with increasing age and increasing Deyo-CCI. Female sex (OR: 1.19; 95% CI: 1.12–1.27, $P < 0.001$) was also an independent predictor of complications.

In univariate analysis, weekend admissions had a higher rate of complications. Upon further investigation, we found that this

Table 3 Independent predictors of CRT implantation complications

Predictor	P-value	Odds ratio* (95% CI)
Age		
18–54	Ref	Ref
55–64	0.952	1.01 (0.89–1.14)
65–74	0.024	1.16 (1.02–1.32)
75–84	<0.001	1.29 (1.13–1.47)
≥85	<0.001	1.40 (1.19–1.64)
Female	<0.001	1.19 (1.12–1.27)
Elective admission	<0.001	0.61 (0.57–0.66)
Deyo-CCI		
0–1	Ref	Ref
2–4	0.017	1.08 (1.02–1.16)
≥5	<0.001	1.22 (1.09–1.37)

Model c-statistics: 0.67 (0.66–0.68).

*Adjusted for insurance status, weekend admission, hospital bedsize, hospital region, hospital teaching status, and calendar year.

‘weekend effect’ was due to a higher proportion of non-elective admissions on weekends (89% on weekends vs. 45% on weekdays). After adjusting for the observed interaction, only elective admission remained a significant independent predictor of complications (OR: 0.61; 95% CI: 0.57–0.66, $P < 0.001$).

Discussion

This study reports trends of in-hospital CRT device implantations from 2003 to 2013 in the U.S. The results demonstrate an increase in the comorbidity index and frequency of in-hospital complications. In-hospital mortality and length of stay remained unchanged over the study period.

The mean (SEM) age of patients receiving CRT implants was 70.15 (0.11) and women comprised 29% of the total population. These demographic characteristics are in line with those published for clinical trials.^{1–3} The mean age increased over the study period ($P = 0.02$), driven mainly by an increase in the mean age of patients receiving CRT-P. A recent study reported advanced age as an independent predictor for CRT-P device selection.¹³ Patients receiving CRT-D devices comprised approximately 86% of the total CRT implantations in the present study, which is in the higher range of the proportions published using European registries.¹⁴

Statistical analysis revealed an overall in-hospital complication rate of 6.11%, similar to those reported in randomized clinical trials.^{3,15,16} In the CARE-HF trial, adverse events occurred in 10% of patients within the first 24 h of implantation.¹⁷ In a study of Medicare beneficiaries from 2006 to 2010 using NCDR registry data, 6.5% of CRT-D recipients had at least one device-related complication.¹⁸ While direct comparisons are not possible for every complication, similarities do exist between the present findings and previously reported clinical trials. Jamerson *et al.*¹⁵ investigated major procedure-related adverse events within the first 30 days of CRT implantation in women vs. men in the MADIT-CRT trial. They reported adverse events in 6.3% of

women, comparable to 6.8% of women in our population. Importantly, the adverse event rates reported in this study reflect only inpatient procedural complications. Results of 30-day post-procedural complications could not be estimated, given the nature of the database.

Cardiac perforation is one of the most serious complications related to CRT implantation. It is also associated with an increase in the rate of other major complications, length of stay, and in-hospital mortality.¹⁹ In this study, the rate of pericardial complications (i.e. cardiac perforation) increased significantly. This increase was mainly driven by the CRT-D population, which is concordant with other studies that have reported an increase in the risk of perforation with an increase in the number of leads.^{20,21} Female gender and older age are also associated with an increased risk of cardiac perforation due to thinner chamber wall thickness in those populations.¹⁹ Correspondingly, in our study, women had higher rates of pericardial complications (1.09% of females vs. 0.47% of males, $P < 0.001$). Body mass index (BMI) has also been reported to be a significant predictor for early procedure-related complications in females.¹⁵ Consistent with this and other studies,^{15,22} both female sex and older age were associated with higher odds of developing any complication. This fact, along with a significant rising trend in the age of patients and the proportion of females undergoing CRT implantation over the study period, may account for the overall rise we observed in complication rates.

Device pocket haematoma and haemorrhage are among the most common complications of CRT implantation. This is in part due to the high proportion of CRT candidates who are under anticoagulant therapy for cardiac comorbidities, in particular atrial fibrillation and atrial flutter. In our study, an increasing trend was observed in haematoma/haemorrhage, alongside an 11% increase in the proportion of CRT candidates who had a history of atrial fibrillation or atrial flutter (from 34.99% in 2003 to 46.26% in 2013, $P < 0.001$). Management of haematoma/haemorrhage may necessitate temporary interruption of anticoagulation therapy, which could have significant ramifications for a population already at risk for thrombo-embolic events.^{23,24} Haematoma has also been associated with an increased risk of infection in recipients of cardiac devices.^{25,26} This could serve as a partial explanation for the observed increase in the rate of post-operative infections during our study period.

Pneumothorax complications following cardiac device implantation have been reported to occur in 0.6 to 1.9% of procedures.^{27–29} In this study, pulmonary complications (i.e. pneumothorax) occurred in 1.48% of all CRT procedures. CRT-P recipients had higher pulmonary complications compared with CRT-D recipients. This could be because the CRT-P population consisted of more females and older patients, characteristics which have been reported as predictors of pneumothorax complications in cardiac device recipients.²⁸

The increase in some complications is also potentially attributable to a higher rate of comorbid conditions over time. From 2003 to 2013, a steady increase was observed in the mean CCI of both groups, as well as the number of patients with two or more comorbidities (Deyo-CCI ≥ 2). Deyo-CCI was a significant independent predictor of in-hospital complications. Previous studies have documented the association between preexisting comorbidities as important risk factors for post-implantation complications.³⁰ In addition, increases in

comorbidities have been linked with an increased rate of infection in CRT recipients.³¹ These findings indicate that, while the use of CRT has expanded, strategies to reduce associated complications are needed.

Previous studies have reported weekend admission (aka the 'weekend effect') and non-elective admission as predictors of mortality and morbidity among hospitalized cardiovascular patients.^{21,32,33} While weekend admissions had a higher rate of complication in this study, this effect was in fact due to the high proportion (89%) of non-elective admissions on weekends. Ultimately, elective admission was the only type of admission that was found to be an independent predictor of complications. This is likely because elective patients are more stable and there is more time to prepare the procedure.

The overall in-hospital mortality rate during the study period was 0.76%. There was no uniform trend in the rate of mortality, even though Deyo-CCI increased significantly. Recipients of CRT-P devices had a higher overall mortality rate in comparison to CRT-D recipients (1.08% vs. 0.7%, $P < 0.001$).

The present study has several limitations. First, data were collected from an administrative database, which may have errors associated with coding inaccuracies. Second, there is the potential for selection bias, given that this study is retrospective and limited to inpatient procedures, and there has been an increase in outpatient CRT implantations in recent years. Third, the NIS does not provide a way to trace the progression of events during a given hospital stay. Therefore, in contrast to outpatient care, it is possible that some patients may have received CRT therapies at the end of treatment for another reason of admission (e.g. decompensated CHF) than solely a stay for CRT implantation. This could partly explain the lengthier stays observed. Fourth, the present study was unable to capture complications that occurred after hospital discharge. Nevertheless, results from recent studies have shown that most complications of CRT implantation occur within 24 h, therefore increasing the applicability of our findings.¹⁷ Fifth, several factors that could affect complication rate are not provided by the NIS: duration of procedure, re-intervention, device explants, and medical management (e.g. anticoagulants). In addition, we could not include operator volume in our analyses because operator ID was not provided for over half the discharges in this dataset. Sixth, the New York Heart Association (NYHA) classification could not be studied, since it is not provided by the NIS. Recent changes in heart failure guidelines regarding preventive CRT therapy in NYHA class II patients could have affected the trends in CRT implantation in the final two years of this study.³⁴ Even so, these changes might have affected outpatient procedures more than inpatient ones, given that NYHA II patients are more likely to be implanted on an outpatient basis.

Conclusion

In summary, this study represents real-world experience in a large population of patients undergoing inpatient CRT implantation in the U.S. from 2003 to 2013. While year-to-year fluctuations in procedure volumes were observed, the average number of implants changed very little. However, the number and severity of comorbidities, particularly in older age groups, increased significantly. These changes, accompanied by an increase in the rate of some procedural

complications, underscore the need for strategies to reduce periprocedural risks in this patient population.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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