Real-world clinical burden among patients with and without heart failure worsening after cardiac resynchronization therapy

Eugene S. Chung, John Rickard, Xiaoxiao Lu, Maral DerSarkissian, Miriam L. Zichlin, Hoi Ching Cheung, Natalia Swartz, Alexandra Greatsinger, and Mei S. Duh

The Lindner Clinical Research Center at The Christ Hospital, Cincinnati, OH, USA; Cleveland Clinic, Cleveland Heights, OH, USA; Medtronic Global CRHF Headquarters, Mounds View, MN, USA; Analysis Group, Boston, MA, USA

ABSTRACT
Objective: Cardiac resynchronization therapy (CRT) can improve cardiac function in patients with heart failure (HF); however, in some patients, HF worsens despite CRT. This study characterized the long-term clinical burden of patients with and without heart failure worsening (HFW) within 6 months post CRT implantation.

Methods: A claims database (2007–2018) was used to identify two cohorts of adults: those with HFW within 180 days post-CRT and those with no HFW (NHFW). The evaluated clinical outcomes were cardiovascular events/complications, HF-related interventions, hospice enrollment, and all-cause mortality. Inverse probability of treatment weighting (IPTW) was used to adjust for confounders; adjusted comparisons were assessed using weighted Cox proportional hazard ratios (HRs).

Results: Among the 12,753 adults analyzed (HFW: N = 4,785; NHFW: N = 7,968), the mean age was 72 years and the mean duration of follow-up was approximately 2 years. The clinical burden was greater for HFW than for NHFW in terms of all-cause mortality (19.7% vs. 12.1%) and occurrence of atrial fibrillation (57.4% vs. 51.2%). In the IPTW-adjusted Cox proportional hazard analyses, patients with HFW had a 54% higher average hazard of experiencing all-cause mortality compared to NHFW (adjusted average HR = 1.54, 95% confidence interval [CI]: 1.41–1.70; p < .001). Of the clinical events experienced by ≥5% of patients, the greatest differences in average hazard were for HF decompensation (adjusted average HR = 1.83, 95% CI: 1.60–2.09) and HF decompensation or death (HR = 1.63, 95%CI: 1.50–1.77).

Conclusion: Patients with early HFW post-CRT experienced a significantly higher clinical burden than those without HFW. Vigilance for signs of worsening HF in the first 6 months post-CRT is warranted.

Introduction
Heart failure (HF) is a chronic and progressive condition characterized by impaired cardiac filling and contraction. In addition to well-established pharmacologic interventions, cardiac resynchronization therapy (CRT) can improve heart contractility and is recommended by the American College of Cardiology/American Heart Association for symptomatic patients with HF. While CRT can reduce HF-related mortality and hospitalizations, 30%–50% of patients do not improve or stabilize after CRT and may be vulnerable to HF worsening (HFW), which is associated with poor prognosis and increased risks of mortality and hospitalizations compared to CRT recipients with no HFW (NHFW). A number of studies have compared the clinical outcomes of CRT responders and non-responders; however, these have been limited by inconsistencies due to variable definitions of CRT response and the small size of patient populations, which need to be addressed to clearly inform healthcare stakeholders and direct efforts to improve the clinical management of HF. Furthermore, early indications of the response to CRT that predict prognosis can guide the optimization of patient care.

Real-world studies using large, nationally representative patient samples can provide insight into the different outcomes of those who experience HF improvement/stabilization or worsening in response to CRT, especially if such patients can be identified soon after CRT. The present study used a large commercial claims dataset to evaluate early response to (i.e. within 6 months of) CRT and how this relates to long-term clinical course. Specifically, we used a previously published claims-based algorithm to compare clinical outcomes between HFW and NHFW patients at 6 months post-CRT.
Methods

Data source

The Optum Clinformatics® Data Mart Database (CDM; January 2007 to December 2018) was used for this study. The CDM contains insurance data for 15–19 million beneficiaries of commercial and Medicare Advantage health plans annually across all United States (US) census regions. Specifically, the database includes medical and pharmacy claims, member eligibility, and inpatient confinements. CDM data have been statistically de-identified using the expert determination method in order to comply with the Health Insurance Portability and Accountability Act, and are managed in accordance with the Optum customer data use agreements16.

Study design

This retrospective cohort study was based on enrollment data, medical claims, and pharmacy claims (Figure 1). The 180-day interval preceding the first implantation of the CRT device was defined as the baseline period. The 180-day period that began on the date of implantation was the response assessment period, with events occurring during this time used to determine HFW or NHFW (as a proxy for CRT response or non-response, respectively; additional details below). The index date was defined as the day following the date of first implantation (i.e. day 181). The follow-up period ranged from the index date to the end of the patient’s continuous eligibility in their insurance plan, end of data availability (December 31, 2018), or death, whichever occurred first.

Sample selection

Patients were eligible for inclusion in this study if they met the following criteria: aged ≥18 years at the index date with ≥1 implantation of a CRT pacemaker (CRT-P, Current Procedural Terminology [CPT] 33208 concurrent with 33225) or CRT defibrillator (CRT-D, CPT 33249 concurrent with 33225), and continuous insurance eligibility during the baseline period through ≥90 days of follow-up (i.e. ≥270 days of continuous insurance data availability after CRT was required). Patients were excluded if they died on or before their index date, their sex was unknown, or they had evidence of implantation with another cardiac device at any time, including implantable cardioverter defibrillators, insertable cardiac monitoring devices, and single-chamber pacemakers15.

We used a claims-based algorithm to identify patients with HF worsening following CRT as a proxy for non-response, as most clinical criteria for CRT response vs. non-response are unavailable in claims data (e.g. NYHA class and quality of life). HFW has been used previously as an indicator of patients’ response to CRT17,18, and the specific algorithm used in the present study to identify patients with HFW was developed based on three previously published studies assessing CRT response or HFW10,18,19.

In the present study, patients meeting all of the inclusion criteria were categorized into two mutually exclusive cohorts: HFW or NHFW in the 6 months following CRT implantation, using previously described criteria15. A 6-month follow-up is often used for post-CRT response assessment of HFW20 based on the PROSPECT trial17, which defined a positive response to CRT as an improved clinical composite score and ≥15% reduction in left ventricular end-systolic volume at 6 months vs. baseline. Patients were classified as having HFW if they had any of the following claims during the response assessment period: (1) de novo diagnoses of ventricular tachycardia or ventricular fibrillation on ≥2 separate, non-consecutive days during the same inpatient stay; (2) hospitalization associated with a cardiac event (i.e. cardiac arrest, congestive HF, or myocardial infarction); (3) de novo hospitalization related to AF; (4) de novo hemodialysis; and (5) intravenous diuretics, intravenous vasodilators, ultrafiltration, mechanical circulatory support (MCS), mechanical ventilation, positive inotropes, or intensive care unit stays.

Baseline patient and disease characteristics

The following patient characteristics were described at the index date: sex, age, geographic region, insurance type, year

![Figure 1](https://example.com/figure1.png)

Figure 1. Study design scheme. CRT: cardiac resynchronization therapy; HF, heart failure. Note: (1). Patients were determined to have HF worsening or no HF worsening based on medical and pharmacy claims during the response assessment period (the 180-day period beginning on the date of the first CRT device implantation claim). Diagnosis codes, procedure codes, medication codes, and place of service codes were used to identify HF worsening.
of the index date, and type of provider for CRT procedure. Patient clinical characteristics evaluated during the baseline period included congestive HF, comorbidities (i.e. hypertension, dyslipidemia, diabetes, AF, ischemic heart disease, left bundle branch block (LBBB), chronic kidney disease, atrioventricular block, or myocardial infarction), the Quan–Charlson Comorbidity Index (CCI), and cardiac medications (i.e. beta-blockers, loop diuretics, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers). Monthly all-cause healthcare costs from the payer perspective were approximated as standardized cost minus coinsurance, copay, and deductible amounts for medical services and as standardized cost minus copay and deductible amounts for pharmacy claims. Costs were inflated to 2018 US dollars for analyses. To identify any medication use during the baseline period, codes in medical service claims and national drug codes in pharmacy claims from the Healthcare Common Procedure Coding System (HCPCS) were used.

**Outcomes**

Clinical outcomes assessed during the follow-up period included cardiovascular events/complications (i.e. AF, myocardial infarction, HF decompensation, and cardiac arrest), HF-related interventions (i.e. mechanical circulatory support, mechanical ventilation, and use of positive inotropic agents), hospice care, and all-cause mortality. Cardiovascular events/complications were identified using the International Classification of Diseases, 9/10th Revision diagnosis and procedure codes; CPT and HCPCS codes in medical claims, and generic product identifiers in pharmacy claims (Supplemental Table 1). HF decompensation was identified by intravenously administered diuretics or positive inotropic agents in any setting on days with any claim associated with congestive HF diagnoses (Supplemental Table 2). A composite endpoint of HF decompensation or death was also assessed. Hospice care was identified using claims for the hospice-associated place of service, type of service, provider category, and revenue codes. HF-related hospitalization was not assessed as an outcome as hospitalization for a cardiac event or de novo hospitalization related to AF during the response assessment period constituted the definition of HFW.

**Statistical analysis**

Inverse probability of treatment weighting (IPTW) was used to adjust for potential confounding and ensure a balanced distribution of covariates at baseline between cohorts21. A propensity score (PS) was calculated for each patient using a logistic regression model to approximate the probability of each individual experiencing HFW based on baseline characteristics. The PS was used to compute the weight for each patient, which reflected the inverse of their probability of being in their respective cohorts given their baseline characteristics (1/PS for HFW and 1/1 – PS for NHFW). The following covariates were included in the PS model as predictors: sex, age at index date, geographic region, insurance plan type, year of index date, type(s) of healthcare provider involved with the CRT procedure, Quan–CCI, type of congestive HF diagnosis, select comorbidities, select medications, and all-cause total monthly per-patient payer-paid healthcare costs during the baseline period. Stabilized weights were estimated and truncated at the 1st and 99th percentiles to minimize variability.

Patient characteristics assessed during the baseline period were compared between cohorts using standardized mean differences (SMDs) before and after IPTW weighting. A standardized mean difference (SMD) <10% between the HFW and NHFW cohorts was deemed to be inconsequential21.

Time-to-event analyses were only conducted for events experienced by ≥5% of patients. The unadjusted median time to events was estimated with the Kaplan–Meier method, and p-values were calculated based on the log-rank test. Adjusted comparisons were performed using a weighted Cox proportional hazards model. Potential violations of the proportional hazards assumption were observed for three clinical outcomes (all-cause death, HF decompensation, and the composite outcome of HF decompensation or death) based on visual inspection of Schoenfeld residual plots and the significance of the treatment-by-time interaction term. Given the possibility of non-proportional hazards, average hazard ratios (HRs) were used to compare the average hazard of each clinical event between the HFW and NHFW cohorts during the entire follow-up period. The 95% confidence intervals (CIs) and p-values were calculated using a robust variance estimator.

**Results**

**Sample selection**

A total of 12,753 patients were included in the study. Of these patients, 4,785 (37.5%) were classified as HFW and 7,968 (62.5%) were classified as NHFW (Supplemental Table 3).

**Baseline patient and disease characteristics**

Across the two cohorts, the mean age was ~72 years and about one-third of patients were female. In the unweighted cohorts, a numerically higher proportion of HFW patients had a year of index date between 2007 and 2012, while a higher proportion of NHFW patients had a year of index date between 2013 and 2018 (Table 1). A larger proportion of HFW patients than NHFW patients had congestive HF of at least one type (i.e. left, systolic, diastolic, combined systolic and diastolic, other, or unspecified) during the baseline period (SMD: 15.4%). The HFW cohort had a significantly higher mean Quan–CCI, indicating that the patients had worse health at baseline than those in the NHFW cohort (3.4 vs. 3.0, SMD: 22.0%). A larger proportion of patients in the HFW cohort were prescribed loop diuretics during the baseline period (60.8% vs. 51.6%, SMD: 18.5%). The mean total payer-paid healthcare costs per month were significantly higher in the HFW cohort than in the NHFW cohort during the baseline period (mean: $7,619 vs. $5,766, SMD: 17.0%).
### Table 1. Patient characteristics by heart failure worsening status during the baseline period

| Demographics at index date | All patients (N = 12,753) | HF worsening (N = 4,785) | No HF worsening (N = 7,968) | Standardized mean difference |
|---------------------------|-----------------------------|--------------------------|----------------------------|-----------------------------|
| Sex, n (%)                |                             |                          |                            |                             |
| Female                    | 4,277 (33.5%)               | 1,662 (34.7%)            | 2,615 (32.8%)              | 4.0%                        |
| Male                      | 8,476 (66.5%)               | 3,123 (65.3%)            | 5,353 (67.2%)              | 4.0%                        |
| Age, years, mean (SD) n (%)| 72.4 (10.4)                 | 71.9 (10.6)              | 72.7 (10.3)                | 7.2%                        |
| 18–34                     | 48 (0.4%)                   | 19 (0.4%)                | 29 (0.4%)                  | 0.5%                        |
| 35–44                     | 151 (1.2%)                  | 63 (1.3%)                | 88 (1.1%)                  | 1.9%                        |
| 45–54                     | 590 (4.6%)                  | 240 (5.0%)               | 350 (4.4%)                 | 2.9%                        |
| 55–64                     | 1,831 (14.4%)               | 757 (15.4%)              | 1,094 (13.7%)              | 4.7%                        |
| 65+                       | 10,133 (79.5%)              | 3,726 (77.9%)            | 6,407 (80.4%)              | 6.3%                        |
| Geographic region, n (%)  |                             |                          |                            |                             |
| Northeast                 | 1,075 (8.4%)                | 480 (10.0%)              | 595 (7.9%)                 | 9.1%                        |
| South                     | 5,204 (40.8%)               | 2,039 (42.6%)            | 3,165 (40.7%)              | 7.2%                        |
| Midwest                   | 3,644 (28.6%)               | 1,374 (28.7%)            | 2,270 (28.5%)              | 0.5%                        |
| West                      | 2,754 (21.6%)               | 865 (18.1%)              | 1,893 (23.7%)              | 13.9%                       |
| Unknown                   | 76 (0.6%)                   | 27 (0.6%)                | 49 (0.6%)                  | 0.7%                        |
| Insurance type, n (%)     |                             |                          |                            |                             |
| Other                     | 4,470 (35.1%)               | 1,666 (34.8%)            | 2,804 (35.2%)              | 0.8%                        |
| HMO                       | 4,412 (34.6%)               | 1,501 (31.4%)            | 2,911 (36.5%)              | 10.9%                       |
| POS                       | 2,011 (15.8%)               | 822 (17.2%)              | 1,189 (14.9%)              | 6.2%                        |
| POS (continued)           |                              |                          |                            |                             |
| 1,038 (8.1%)              | 434 (9.1%)                  | 604 (7.6%)               | 367 (4.6%)                 | 5.4%                        |
| Indemnity                 | 495 (3.9%)                  | 208 (4.3%)               | 172 (2.2%)                 | 3.8%                        |
| EPO                       | 324 (2.5%)                  | 152 (3.2%)               | 172 (2.2%)                 | 6.3%                        |
| Multiple                  | 3 (0.0%)                    | 2 (0.0%)                 | 1 (0.0%)                   | 1.0%                        |
| Year of index date, n (%) |                             |                          |                            |                             |
| 2007                      | 6 (0.0%)                    | 4 (0.1%)                 | 2 (0.0%)                   | 2.5%                        |
| 2008                      | 591 (4.6%)                  | 287 (6.0%)               | 304 (3.8%)                 | 10.1%                       |
| 2009                      | 675 (5.3%)                  | 335 (7.0%)               | 340 (4.3%)                 | 11.9%                       |
| 2010                      | 750 (5.9%)                  | 360 (7.5%)               | 390 (4.9%)                 | 10.9%                       |
| 2011                      | 973 (7.6%)                  | 418 (8.7%)               | 555 (7.0%)                 | 6.6%                        |
| 2012                      | 1,038 (8.1%)                | 436 (9.1%)               | 602 (7.6%)                 | 5.6%                        |
| 2013                      | 1,127 (8.8%)                | 411 (8.6%)               | 716 (9.0%)                 | 1.4%                        |
| 2014                      | 1,150 (9.0%)                | 405 (8.5%)               | 745 (9.3%)                 | 3.1%                        |
| 2015                      | 1,257 (9.9%)                | 412 (8.6%)               | 845 (10.6%)                | 6.8%                        |
| 2016                      | 1,571 (12.3%)               | 506 (10.6%)              | 1,056 (13.4%)              | 8.6%                        |
| 2017                      | 1,773 (13.9%)               | 605 (12.6%)              | 1,168 (14.7%)              | 5.9%                        |
| Time to HF worsening, days, median [95% CI] | 15 [13, 17] | -- | -- | -- |

| Time to HF worsening, days, median [95% CI] | 15 [13, 17] | -- | -- | -- |

| Type(s) of provider for CRT procedure, n (%) | 7,695 (60.3%) | 3,096 (62.9%) | 4,699 (58.8%) | 8.1% |
| Cardiothoracic surgeon | 4,155 (32.6%) | 1,374 (28.7%) | 2,781 (34.9%) | 13.3% |
| Cardiac electrophysiologist | 1,772 (13.9%) | 688 (14.4%) | 1,084 (13.6%) | 2.2% |
| Non-participating area hospital | 1,275 (10.0%) | 421 (8.8%) | 854 (10.7%) | 6.5% |
| Cardiovascular disease specialist | 778 (6.1%) | 315 (6.6%) | 463 (5.8%) | 3.2% |
| Internist/general internist | 325 (2.5%) | 120 (2.5%) | 205 (2.6%) | 0.4% |
| Internal medicine specialist | 308 (2.4%) | 69 (1.4%) | 239 (3.0%) | 10.6% |
| Family practitioner | 263 (2.1%) | 82 (1.7%) | 181 (2.3%) | 4.0% |
| Other | 1,118 (8.8%) | 339 (7.1%) | 779 (9.8%) | 9.7% |

| Clinical characteristics during baseline period n (%) | 3.2 (1.6) | 3.4 (1.7) | 3.0 (1.5) | 22.0% |
| Congestive heart failure, n (%) | 484 (3.8%) | 143 (3.0%) | 341 (4.3%) | 6.9% |
| 0 | 169 (1.3%) | 47 (1.0%) | 122 (1.5%) | 4.9% |
| 2 to 4 | 9,998 (78.4%) | 3,619 (75.6%) | 6,379 (80.1%) | 10.7% |
| 5 | 2,102 (16.5%) | 976 (20.4%) | 1,126 (14.1%) | 16.6% |

(continued)
Continued.

Table 1. Continued.

| Comorbidities, n (%) | Unadjusted | HF worsening | No HF worsening | Standardized mean differencea | IPTW-adjusted1 | HF worsening | No HF worsening | Standardized mean differencea |
|----------------------|------------|--------------|----------------|--------------------------------|----------------|--------------|----------------|--------------------------------|
| Ischemic heart disease | 5,047 (39.6%) | 2,055 (42.9%) | 2,992 (37.6%) | 11.0%* | 1,888 (39.6%) | 3,152 (39.6%) | 0.0% | 0.0% |
| Atrial fibrillation | 7,507 (44.8%) | 2,252 (47.1%) | 3,553 (43.4%) | 7.4% | 2,146 (45.0%) | 3,568 (44.8%) | 0.4% | 0.4% |
| Myocardial infarction | 1,785 (14.0%) | 785 (16.4%) | 1,000 (21.3%) | 11.0%* | 668 (14.0%) | 1,110 (13.9%) | 0.2% | 0.2% |
| Atrial ventricular block | 2,657 (20.8%) | 960 (20.1%) | 1,697 (21.3%) | 3.0% | 1,005 (21.1%) | 1,663 (20.9%) | 0.5% | 0.5% |
| Left bundle branch block | 5,534 (43.6%) | 2,010 (42.0%) | 3,544 (44.5%) | 0.7% | 2,074 (43.5%) | 3,471 (43.6%) | 0.1% | 0.1% |
| Hypertensive heart disease | 2,160 (16.9%) | 856 (17.9%) | 1,304 (16.4%) | 4.0% | 804 (16.9%) | 1,344 (16.9%) | 0.0% | 0.0% |
| Hypertension | 10,562 (82.8%) | 4,038 (84.4%) | 4,524 (50.3%) | 6.7% | 3,993 (82.6%) | 5,689 (82.7%) | 0.3% | 0.3% |
| Cerebrovascular disease | 2,105 (16.5%) | 886 (18.5%) | 1,219 (15.3%) | 8.6% | 796 (16.7%) | 1,312 (16.5%) | 0.6% | 0.6% |
| Diabetes | 5,541 (43.4%) | 2,298 (48.0%) | 3,243 (40.7%) | 14.8%* | 2,067 (43.3%) | 3,453 (43.4%) | 0.0% | 0.0% |
| Major depressive disorder | 807 (6.3%) | 298 (6.2%) | 509 (6.4%) | 0.7% | 303 (6.3%) | 505 (6.3%) | 0.0% | 0.0% |
| Dyslipidemia | 9,361 (73.4%) | 3,575 (74.7%) | 5,786 (72.6%) | 4.7% | 3,502 (73.4%) | 5,847 (73.4%) | 0.1% | 0.1% |
| Chronic kidney disease | 3,604 (28.3%) | 1,504 (31.4%) | 2,100 (26.4%) | 11.2%* | 1,342 (28.1%) | 2,245 (28.2%) | 0.1% | 0.1% |
| Chronic obstructive pulmonary disease | 3,149 (24.7%) | 1,347 (28.2%) | 1,802 (22.6%) | 12.7%* | 1,177 (24.7%) | 1,963 (24.7%) | 0.0% | 0.0% |

Medication during baseline period, n (%) |

| Beta-blockers | 9,227 (72.4%) | 3,466 (72.5%) | 5,759 (72.3%) | 0.4% | 3,444 (72.2%) | 5,759 (72.3%) | 0.2% | 0.2% |
| Loop diuretics | 7,019 (55.0%) | 2,907 (60.8%) | 4,112 (51.6%) | 15.8%* | 2,637 (55.3%) | 4,387 (55.1%) | 0.4% | 0.4% |
| Angiotensin converting enzyme inhibitors | 6,203 (48.6%) | 2,361 (49.3%) | 3,842 (48.2%) | 2.2% | 2,318 (48.6%) | 3,871 (48.6%) | 0.0% | 0.0% |
| Angiotensin receptor blockers | 2,982 (23.4%) | 1,099 (23.0%) | 1,883 (23.6%) | 1.6% | 1,122 (23.5%) | 1,966 (23.4%) | 0.2% | 0.2% |
| Sodium-glucose co-transporter 2 inhibitors | 61 (0.5%) | 20 (0.4%) | 41 (0.5%) | 1.4% | 21 (0.4%) | 37 (0.3%) | 0.4% | 0.4% |

Payer paid healthcare costs during baseline period, per monthb, mean (SD) |

| Total | 6,461 (510,718) | 5,760 (511,758) | 5,576 (59,956) | 17.0%* | 5,440 (510,485) | 6,446 (511,009) | 0.1% | 0.1% |
| Medical | 6,193 (510,675) | 5,709 (511,730) | 5,523 (59,922) | 16.4%* | 5,619 (510,433) | 6,191 (510,974) | 0.2% | 0.2% |
| Pharmacy | 269 (507) | 310 (507) | 244 (507) | 9.5% | 291 (507) | 254 (507) | 5.3% | 5.3% |

Abbreviations. CI, confidence interval; CRT, cardiac resynchronization therapy; EPO, exclusive provider organization; HF, heart failure; HMO, health maintenance organization; IPTW, inverse probability of treatment weighting; IQR, interquartile range; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

Notes:
1. The baseline period was the 180-day period before the first CRT device implantation claim.
2. Patients were defined as having HF worsening or no HF worsening based on diagnoses, procedures, and medications filled during the response assessment period (the 180-day period beginning on the date of the first CRT device implantation claim).
3. IPTW was conducted with stabilized weights generated using the following covariates: sex, age at index date, region of residence, type of insurance plan, year of index date, type(s) of healthcare provider associated with CRT procedure, Quan–Charlson Comorbidity Index, type of congestive HF diagnosis, comorbidities of interest, medications of interest, and total per-patient payer paid healthcare costs during the baseline period. To minimize variability, stabilized weights were limited to the 1st and 99th percentiles.
4. For each variable, a standardized mean difference < 10% was considered an inconsequential imbalance between cohorts. In the IPTW-adjusted sample, weighted standardized mean differences were quantified from each patient’s stabilized weight. Standardized mean differences > 10% in magnitude are denoted with “*”.
5. Time from the date of the first CRT device implantation claim to the first HF worsening event during the response assessment period was evaluated by Kaplan–Meier analysis in patients with ≥1 HF worsening event during the 6-month period after CRT implantation.
6. The index date was the day after the end of the response assessment period.
7. A patient could be flagged for multiple healthcare providers; therefore, categories may not sum to 100%.
8. Quan-Charlson Comorbidity Index computed according to the methods outlined in: Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel J, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 Countries. Am J Epidemiol 2011;173(6):676–82.
9. A patient may be flagged for multiple types; therefore, categories may not sum to 100%.
10. Derived estimated amounts paid by the payer were calculated as standardized cost less coinsurance, copay, and deductible amounts for medical services and as standardized cost minus copay and deductible amounts for pharmacy claims. Amounts are reported in 2018 US dollars.
After IPTW, patient demographics, clinical characteristics, and payer-paid healthcare cost amounts during the baseline period were balanced between the HFW and NHFW cohorts (all SMDs <10%).

Outcomes

During the response assessment period, the three most common events experienced by patients in the HFW cohort were hospitalization associated with congestive HF (49.9%), intensive care unit stay (45.5%), and de novo diagnosis of ventricular tachycardia (15.3%) (Supplemental Table 4). The mean length of follow-up was similar between the HFW and NHFW cohorts (24.3 vs. 26.0 months; Table 2). Events experienced by the largest proportion of patients in the overall sample during the follow-up period were AF (53.5%), the composite outcome of HF decompensation or death (19.7%), hospice care (15.8%), and all-cause mortality (15.0%). Less than 5% of patients had cardiac arrest (4.7%), use of MCS (1.4%), or use of positive inotropic agents (1.3%).

All evaluated events were experienced by a higher proportion of patients with HFW. A larger proportion of patients in the HFW cohort died compared to the NHFW cohort (19.7% vs. 12.1%; average HR: 1.54, p < .001). AF was the most commonly experienced event in both cohorts, with a larger proportion of patients in the HFW cohort experiencing the event (57.4% vs. 51.2%). Large unadjusted differences in the proportion of patients in the HFW and NHFW cohorts with HF decompensation (9.9% vs. 5.1%), the composite outcome of HF decompensation or death (26.5% vs. 15.7%), hospice care (22.3% vs. 11.9%), and use of mechanical ventilation (11.3% vs. 6.6%) were observed.

Median time to AF among patients with HFW was half that of patients with NHFW (median [95% CI]: 9.8 [8.9–11.0] months vs. 18.3 [16.4, 20.2] months, p < .001; Table 2). Similarly, median times to all-cause death and the composite outcome of HF decompensation or death were >2 years shorter in the HFW cohort than in the NHFW cohort (90.4 [77.7–98.0] vs. 115.1 [101.1–not reached] months and 67.7 [61.0–71.4] vs. 96.7 [85.4, not reached] months, respectively; Table 2 and Figures 2–4).

In the IPTW-adjusted Cox proportional hazards analyses comparing the HFW and NHFW cohorts, average HRs over the entire follow-up period were significantly higher than 1 for all examined clinical events (all p < .02; Figure 5). Compared to patients with NHFW, those with HFW had a 54% higher average hazard of experiencing all-cause death during the entire follow-up period (adjusted average HR: 1.54 [95% CI: 1.41–1.70], p < .001). Among events experienced by >5% of patients, the largest differences in average hazard were in HF decompensation (adjusted average HR: 1.83 [95% CI: 1.60, 2.09]), HF decompensation or death (HR: 1.63 [95% CI: 1.50–1.77]), and hospice care (adjusted average HR: 1.74 [95% CI: 1.59–1.91]).

Discussion

This real-world, observational, retrospective cohort study was conducted to characterize differences in long-term clinical outcomes between patients with HFW and NHFW soon after CRT in a large, nationally representative US healthcare administrative claims database. The results of this study showed that early post-CRT HFW was associated with significantly higher rates of all-cause mortality, cardiovascular events/complications, hospice care, and non-surgical HF-related interventions. Moreover, patients with HFW had a higher probability of the combination of death or HF decompensation within 5 years of CRT. These results suggest that HFW soon after CRT can identify patients with poor prognosis who warrant close monitoring. Moreover, the high clinical burden of patients with HFW relative to those with NHFW soon after CRT is reflected by the higher economic burden and healthcare resource utilization of patients with non-response to CRT (i.e. with NHFW) evaluated in a separate study15, highlights a critical need to optimize CRT delivery in the early post-procedure phase.

Downstream effects of suboptimal CRT response

Some patients do not respond to or improve after CRT. There are a few possible explanations for a suboptimal response. A retrospective study of 75 patients evaluated >6 months post CRT reported inadequate device settings (47%), suboptimal medical therapy (32%), arrhythmias (32%), and inappropriate lead position (21%) as the most common contributors to a suboptimal response22. As healthcare providers identify patients most likely to benefit from CRT and optimize device setting post-implantation, the rate of non-response to CRT is expected to improve, although universal criteria for quantifying the improvement in clinical outcomes are needed. Variable definitions of CRT and small sample sizes have limited the generalizability of results of previous studies on the clinical burden of non-response to CRT. For example, a real-world retrospective study of patients with a CRT-D who responded to the treatment experienced significantly lower rates of hospitalization for post-implant HF, but the study was conducted at a single center in the US and the study population included just 32 non-responders and 103 responders13. Another retrospective study examining the response to CRT in patients at a single hospital in Korea found that non-responders had a higher incidence of adverse clinical outcomes (defined as all-cause death or HF events requiring hospitalization); in addition to small sample size, the study limited the definition of CRT response to a >15% reduction in left ventricular end systolic volume or ≥10% increase in LVEF14. A prospective registry-based study of non-responders to CRT found that these patients were more likely to have modifications to their medications than responders (55.9% vs. 38.3% of responders; p < .001); additionally, non-responders had significantly higher rates of hospitalization and cardiac death within 6–12 months of CRT device implantation12. An important caveat is that the study did not control for differences between responders
**Table 2. Unadjusted clinical events by heart failure worsening status during the follow-up period – time-to-event analyses.**

| Event                                      | All patients (N = 12,753) | HF Worsening (N = 4,785) | No HF Worsening (N = 7,968) | Log-rank Test P-values |
|--------------------------------------------|---------------------------|--------------------------|----------------------------|------------------------|
| **Length of follow-up, months, mean (SD)** |                           |                          |                            |                        |
| Death, all-cause                           | 25.4 (21.3)               | 24.3 (21.3)              | 26.0 (21.3)                |                        |
| Cardiovascular events/complications        |                           |                          |                            |                        |
| Atrial fibrillation                        | 1,077 (15.8%)             | 935 (19.7%)              | 944 (12.1%)                |                        |
| HF decompensation or death                 | 6,826 (53.5%)             | 2,784 (57.4%)            | 4,078 (51.2%)              |                        |
| Myocardial infarction                      | 2,517 (19.7%)             | 1,266 (26.5%)            | 1,251 (15.7%)              |                        |
| Cardiac arrest                             | 1,253 (9.8%)              | 563 (11.8%)              | 690 (8.7%)                 |                        |
| HF decompensation                          | 886 (6.9%)                | 476 (9.9%)               | 410 (5.1%)                 |                        |
| Cardiac arrest                             | 599 (4.7%)                | 285 (6.0%)               | 314 (3.9%)                 |                        |
| HF-related interventions                   |                           |                          |                            |                        |
| MCS                                        | 174 (1.4%)                | 82 (1.7%)                | 92 (1.2%)                  |                        |
| Mechanical ventilation                     | 1,070 (8.4%)              | 541 (11.3%)              | 529 (6.6%)                 |                        |
| Use of positive inotropic agents           | 165 (1.3%)                | 101 (2.1%)               | 64 (0.8%)                  |                        |
| Hospice care                               | 2,014 (15.8%)             | 1,069 (22.3%)            | 945 (11.9%)                |                        |
| **Time to event, months, median [95% CI]**  |                           |                          |                            |                        |
| Death, all-cause                           | 101.1 [95.0, 114.6]       | 90.4 [77.7, 98.0]        | 115.1 [101.1, NR]          | <.001                  |
| Cardiovascular events/complications        |                           |                          |                            |                        |
| Atrial fibrillation                        | 14.4 [13.3, 15.8]         | 9.8 [8.9, 11.0]          | 18.3 [16.4, 20.2]          | <.001                  |
| HF decompensation or death                 | 80.0 [76.2, 90.8]         | 67.7 [61.0, 71.4]        | 96.7 [85.4, NR]            | <.001                  |
| Myocardial infarction                      | NR [122.6, NR]            | 122.6 [122.6, NR]        | NR [NR, NR]                | <.001                  |
| Cardiac arrest                             | NR [NR, NR]               | NR [110.6, NR]           | NR [NR, NR]                | <.001                  |
| HF-related interventions                   |                           |                          |                            |                        |
| Mechanical ventilation                     | NR [NR, NR]               | NR [NR, NR]              | NR [NR, NR]                | <.001                  |
| Hospice care                               | 2,014 [78.6, NR]          | 1,069 [22.3%]            | 945 [11.9%]                | <.001                  |

Abbreviations. CI, confidence interval; CRT, cardiac resynchronization therapy; HF, heart failure; MCS, mechanical circulatory support; NR, not reached; SD, standard deviation.

Notes:
1. The index date was defined as the day after the end of the response assessment period (the 180-day period beginning on the date of the first CRT device implantation claim). The follow-up period was the period beginning on the index date and ending at the earliest of either the end of continuous insurance eligibility, end of data cut (December 31, 2018), or death. Patients were censored at end of the follow-up period (not censored for death when evaluating all-cause death and the composite endpoint of HF decompensation or death).
2. Patients were determined to have HF worsening or no HF worsening based on diagnoses, procedures, and medications filled during the response assessment period.
3. Outcomes were identified by a combination of diagnoses, procedures, medications, and service settings. HF decompensation was identified by intravenously administered diuretics or positive inotropic agents in any setting on days with any claim associated with congestive HF diagnoses (Supplemental Table 1).
4. Hospice care was identified using claims with place of service, type of service, provider category, and revenue codes associated with hospice.
5. Time from index date to first event was analyzed with the Kaplan–Meier method; the analyses were conducted only for events experienced by ≥5% of patients.

and non-responders at baseline (i.e. before CRT implantation). Although the present study did not compare rates of HF hospitalization as it was included in the definition for HFW, we also found higher all-cause mortality among non-responders than responders over a mean follow-up of 2 years (19.7% vs. 12.1%).

**Interventional options for suboptimal CRT response**

A better understanding of the key characteristics of patients who respond to therapy can ensure that patients implanted with the device achieve the maximum clinical benefit. It is also important to consider all aspects of patient care including the initiation of CRT, clinical stability, the severity of baseline comorbidities, medical history (e.g. use of a ventricular assist device), and the possibility of a heart transplant. A systematic review of 12 studies published between 1995 and 2014 found that LBBB morphology, non-ischemic cardiomyopathy, sinus rhythm (vs. AF), duration of wider QRS, and female sex predicted a better response to CRT-D implantation, although predictors of response to CRT-P implantation were less evident. Optimizing device settings using newer algorithms based on intracardiac electrograms to improve blood flow vs. echocardiography optimization (the gold standard) has resulted in significant improvements in patient outcomes in clinical studies. A prospective, multicenter, double-blind, randomized non-inferiority trial examining the safety and efficacy of a contractility sensor (located within the right atrial lead) reported a response rate of 75% vs. 70.4% in patients with echocardiography optimization (p < .001). Additionally, adaptive CRT—a novel algorithm for CRT pacing involving dynamic optimization of atrioventricular and interventricular delays—was shown to be as safe and effective as echocardiography optimization and was associated with improved response (evidence of AF: 8.7% vs. 16.2%) and reduced mortality (survival rate: 88.3% vs. 83.7%) compared to conventional CRT.

**Strengths**

This study has certain strengths that addressed the limitations of previous studies. First, it used a large patient sample from an administrative claims database that captured information on clinical outcomes spanning 11 years across four geographic regions in the US, which allowed generalizability to patients on commercial insurance plans who received CRT during this time period. Second, the database included detailed information on patient demographics, diagnoses,
and procedures from medical claims and on medication use from pharmacy claims, providing a more comprehensive profile of patients before CRT and allowing the balancing of characteristics between cohorts for adjusted analyses. Third, patients were observed for a mean of 2 years post CRT implantation, allowing a long-term assessment of clinical outcomes that can facilitate clinical management.

Limitations

The findings of this study should be interpreted within the context of specific limitations. First, HFW is an imperfect measure of non-response to CRT; however, it is applicable to claims data and has been used in previous studies [17,31]. Second, the algorithm used in this study to identify HF has not been validated although it was based on published work [10,18,19]. The algorithm classified HFW based on de novo diagnoses (e.g. ventricular tachycardia) and procedures (e.g. hemodialysis); patients with previous diagnoses or procedures that were not observed within the period before data cutoff may have been misclassified, leading to underestimation of the burden of HFW following CRT. Additionally, procedures and medications included in the algorithm may have been used for non-cardiac conditions (e.g. mechanical ventilation for pneumonia); patients may have been misclassified as having HFW based on procedures and use of medications unrelated to HF. Finally, as information on relevant clinical characteristics such as LVEF was not available in the database, we identified clinical outcomes from administrative claims data, which contain diagnostic and procedure...
information only for reimbursement purposes; any potential misclassification of patients as HFW and NHFW with the algorithm due to misspecification of diagnosis, procedure, or drug codes could have resulted in underestimation or overestimation of clinical outcomes associated with HFW. Third, only patients with ≥270 days of continuous insurance data availability following CRT were analyzed, which may have excluded those who were not in sufficiently good health to survive for a long period following CRT. Although we found that HFW following CRT was associated with worse clinical outcomes than NHFW, additional studies are needed to elucidate the associated mechanisms and/or predictors. Furthermore, as we used a US claims database as the data source, our results may not be generalized to patients in other countries. Fourth, residual confounding may have affected adjusted comparisons as only factors recorded in the database could be accounted for, and other clinical covariates related to disease severity (such as LVEF) were not available in claims data. Fifth, there were possible violations of the proportional hazards assumption for some outcomes and consequently, only HRs averaged across the follow-up period were reported, which do not reflect HRs at all discrete time points and may be influenced by the length of the observation period. Sixth, although we used IPTW to balance the two cohorts with respect to baseline characteristics, the HFW cohort had more comorbidities than the NHFW cohort (mean Quan–CCI: 3.4 vs. 3.0), which may have influenced clinical outcomes.

Conclusions
The results of this study demonstrate that HFW soon after CRT implantation is associated with a significantly higher rate of cardiovascular events, most notably HF decompensation and death. Early identification and prevention of HFW in patients who receive CRT can improve the clinical outcome of this patient population.

Transparency
Declaration of funding
This work was supported by Medtronic.

Declaration of financial/other relationships
Eugene S. Chung receives consulting honoraria from Medtronic, Abbott, and ERB Systems. John Rickard has received consulting fees from Medtronic as well as speaking fees and research funding from Abbott. Xiaoxiao Lu was an employee of Medtronic at the time this work was conducted. Maral DerSarkissian, Miriam L. Zichlin, Natalia Swartz, Alexandra Greatsinger, and Mei S. Duh are employees of Analysis Group, a consulting firm that received funding for the analyses that were conducted. Hoi Ching Cheung was an employee of Analysis Group at the time this work was conducted. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions
Study design, clinical input, data interpretation, and manuscript writing and editing: Eugene S. Chung, John Rickard, and Xiaoxiao Lu. Formal
analysis, data interpretation, and manuscript writing and editing: Maral DerSarkissian, Miriam L. Zichin, Hoi Ching Cheung, Natalia Swartz, Alexandra Greasinger, and Mei S. Duh. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and take responsibility for the integrity of the work as a whole.

Acknowledgements

Medical writing support was provided by Gloria DeWalt, an employee of Analysis Group; financial support for this assistance was provided by Medtronic.

Data availability statement

The data analyzed in this study are not publicly available due to licensing agreements with Optum Clinformatics Data Mart Database.

Ethics statement

Not applicable to the de-identified claims data used in this study.

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