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ORIGINAL ARTICLE

Adherence to heart failure management medications following cardiac resynchronization therapy

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ABSTRACT

Objective: The purpose of this study is to assess the real-world impact of cardiac resynchronization therapy (CRT) on adherence to heart failure (HF) medications.

Methods: MarketScan administrative health care claims data from 2008 to 2014 among patients with HF were used. The date of first CRT implantation served as the index date. Adherence to guideline-directed medical therapy (GDMT) classes were compared during pre- and post-index periods using proportion of days covered (PDC). Comparisons between the two periods were made using the Wilcoxon sign-rank test for continuous PDC and McNemar's test for dichotomized PDC.

Results: Increases in medication adherence were observed for major classes of HF GDMT medications. Specifically, adherence to angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), beta blockers (BB), and furosemide increased by 22, 24, 32, and 28% (all $p < .001$), respectively, in the 12 months pre to 12 months post-CRT. Large increases between the pre- and post-CRT period were also observed when considering adherence as dichotomized PDC $\geq$0.80 in the 12 months pre- versus post-CRT.

Conclusion: Adherence to HF medications significantly improved among HF patients post-CRT implantation. Further research is needed to better understand the underlying determinants of this effect, including whether the effect is attributable to factors such as enhanced patient monitoring and improved access to high-quality specialized HF care among patients receiving CRT.

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Introduction

Heart failure (HF), is a clinical syndrome that occurs when the heart loses its ability to sufficiently pump oxygenated blood throughout the body as well as it should due to structural or functional impairment of ventricular filling or blood ejection[1]. HF is a chronic disease that is highly prevalent in the United States (US) among patients 65 and older and is associated with a high burden of health care costs, use of health care services, and productivity loss[2,3].

Medications such as beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) have been shown to decrease morbidity and mortality in HF patients[3–5]. Despite improvements in pharmacotherapy, many patients continue to have persistent symptoms and poor prognosis[6,7]. Cardiac resynchronization therapy (CRT) emerged in the early 2000s as a possible improvement to the standard of care for selected patients with HF when used in combination with traditional pharmacologic therapies[8]. CRT treats patients with HF by correcting intraventricular, interventricular, and atrioventricular conduction delays and improving left ventricle contractility by resynchronizing the right and left ventricles to contract at the same time through biventricular pacing[6,9].

CRT is recommended in selected patients with HF with reduced ejection fraction since it has been shown to reduce HF symptoms, HF hospitalizations, and mortality in randomized controlled trials[8,10–13]. CRT is recommended in addition to guideline-directed medical therapy (GDMT) and implantable cardioverter-defibrillators (ICDs) when indicated for primary or secondary prevention of sudden cardiac death. According to the American College of Cardiology Foundation/American Heart Association HF guidelines, evidence-based care (i.e. GDMT) for HF patients with reduced ejection fraction includes ACE-I or ARBs, BB, and for patients with electrical dyssynchrony (evidenced by wide QRS), CRT alone (CRT-P) or combined with a defibrillator (CRT-D) should be considered[3].

Given the importance of GDMT for management of HF in certain groups of patients, it is important to understand how CRT implantation may be related to adherence to GDMT to further decrease patients' symptoms and morbidity burden.

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This study uses MarketScan administrative health care claims data from 2008 to 2014 to assess the real-world impact of CRT implantation on adherence to the heart failure medications defined as GDMT classes. Specifically, adherence to ACE-I, ARB, BB, and furosemide were compared during pre- and post-index periods using a proportion of days covered (PDC).

Methods

Study design and population

A retrospective, fixed cohort study design utilizing medical, pharmacy, and enrollment claims among HF patients was used to assess adherence to HF medications (i.e., GDMT) pre- and post-CRT implantation. Data from the MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases between 1 January 2008 and 31 December 2014 were used for this study. This large, de-identified healthcare administrative claims database includes demographics, enrollment history, and inpatient, outpatient, and pharmacy claims for employees, their spouses, and their dependents from over 100 employers, health plans, and public organizations[14].

To be included in this study, patients were required to have at least one medical claim for CRT-P or CRT-D identified by International Classification of Diseases, Revision 9 (ICD9) codes. The index date was defined as the first date by which a patient had a medical claim for CRT implantation. Patients were also required to have 6-, 12-, and 24-months of continuous eligibility prior to and following the index date, which defined the pre-index and post-index periods with the respective duration during which adherence was assessed. Only patients aged 18–64 years were included (i.e. Medicare-eligible patients aged 65 years or older who would be covered for prescription drugs through Part D plans that are not captured in MarketScan were excluded), and those with claims for cancer observed at any time in the database or more than 30 days of continuous use of hypersensitivity myocarditis medications or other medications with adverse cardiac reactions (i.e. cobalt, anabolic steroids, chloroquine, clozapine, amphetamine, methylphenidate, and catecholamines) in the pre-index period were excluded[15]. These patients were excluded in order to limit the potential effect of HF or cardiac-related adverse drug events as a result of cancer therapy or other medications. A sensitivity analysis in which patients with cancer and left-ventricle assist devices (LVAD) were included in the study population was also performed. Although CRT is not indicated for patients with right bundle branch block (RBBB), certain patients with RBBB (such as those with concomitant left ventricle intraventricular dyssynchrony or with presence of concomitant left hemiblock), may benefit from CRT implantation[16]. Therefore, in order to provide a comprehensive analysis of all patients receiving CRT in real-world settings, patients with RBBB were included in our sample if they met all other inclusion and exclusion criteria.

GDMT classes under study

Pre- and post-index adherence was assessed for ACE-I, ARB, BB, and furosemide (the latter was used as a proxy for loop-diuretics as a whole, due to it being the most predominantly used agent in the class)[17]. Previous studies assessing adherence have demonstrated that evaluating both individual GDMT and medication regimens can improve the reliability of results in claims studies[18]. As a sensitivity analysis, adherence to GDMT-based HF medication regimens (ACE-I/ARB/direct renin inhibitor [DRI] + BB; ACE-I/ARB/DRI + BB + furosemide) was also assessed.

Study covariates and outcomes

Demographics, including age, gender, geographic region, and clinical characteristics, were summarized for patients during the 6-, 12-, and 24-month pre-index periods. These different length periods were selected because it would allow us to understand the short-, medium-, and long-term impact of CRT on adherence, in order to understand whether medication adherence may change over different periods time. Clinical characteristics assessed during the pre-index period included the Charlson Comorbidity Index (CCI; a measure of severity of underlying clinical conditions), comorbid conditions common among patients with HF based on ICD9 diagnosis codes (i.e., dyslipidemia, coronary heart disease, and hypertension), presence of related cardiovascular conditions, and concomitant medication use.

Adherence to HF GDMT classes was calculated among patients who received at least one day of a specific drug class during both the pre- and post-index period, as evidenced by the presence of pharmacy claims for drugs from the class with at least one days' supply[19]. Adherence was measured by the PDC, calculated as the sum of the number of unique days during which the patient had medication available, divided by a fixed time interval of 6-, 12-, or 24-months as applicable. PDC $\geq$80% was used to define patients who were adherent to therapy[20].

Statistical analyses

Patient baseline demographics and clinical characteristics were described using mean, median, and standard deviation (SD) for continuous variables and frequency counts and proportions for categorical variables. These characteristics were described separately for each cohort defined by the length of the pre- and post-index periods.

Adherence was summarized using the mean, median, and SD along with the proportion of patients with PDC $\geq$ 80%. Adherence in the pre- and post-index periods were compared using the Wilcoxon sign rank test for continuous PDC and McNemar's test for dichotomized PDC in order to account for the paired nature of the data. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and baseline characteristics

Table 1 presents patient demographics and clinical characteristics of the study population evaluated during the 6-, 12-, and 24-month pre and post-index periods. Cohorts of 4500 patients with CRT and $\geq$ 6 months of continuous enrollment pre- and post-index, 2603 patients with $\geq$ 12 months, and 829 with $\geq$ 24 months of continuous enrollment were included in the study. The mean age of subjects in all three cohorts was approximately 56 years (SD of approximately 7 years in each cohort), and more than 66% of subjects in all cohorts were male. Across all cohorts, 48.1–63.3% of patients had dyslipidemia, 35.9–39.8% had diabetes, and 56.6–71.2% had hypertension (Table 1).

Adherence to HF GDMT classes during the pre-index and post-index periods

Figure 1 presents the proportion of patients with PDC $\geq$ 80% for the HF GDMT classes of interest during the 12-month pre- and post-index period. The proportion of patients with PDC $\geq$ 80% for individual medication classes increased consistently and substantially from the 12 months pre-index to the 12 months post-index. The proportion of patients who were adherent to ACE-I increased from 37.2 to 54.6%, ARB increased from 37.3 to 54.8%, BB increased from 34.0 to 58.3%, and furosemide increased from 26.4 to 40.8% in the pre- and post-index periods, respectively (all $p < .001$).

Results for adherence assessed during the 6- and 24-month pre- and post-index periods were similar, and were supported by the analysis of continuous PDC and duration of treatment during the 6-, 12-, and 24-month pre- and post-index periods, presented in Table 2. Mean PDC for HF GDMT classes significantly increased from the pre-index period to the post-index period in each of the 6-, 12-, and 24-month periods. From the 6-month pre- to post-index period, PDC increased 11.9% for ACE-I, 13.6% for ARB, 14.9% for BB, and 16.7% for furosemide (all $p < .001$). During the 12-month pre- and post-index period, PDC increased 22.4% for ACE-I, 23.7% for ARB, 31.6% for BB, and 28.0% for furosemide (all $p < .001$). In addition, during the 24-month pre- and post-index period, PDC increased 37.5% for ACE-I, 38.3% for ARB, 53.2% for BB, and 50.0% for furosemide (all $p < .01$).

The sensitivity analysis of HF medication regimens showed similar results with respect to increasing adherence from pre- to post-CRT implantation (see Appendix Table A1). In addition, the time trend in adherence to medication regimens was assessed, and showed a slight drop in adherence months after CRT implantation; however, the plateau and overall trend in the months following was higher than adherence prior to index (see Appendix Figure A1).

Discussion

This retrospective observational study assessed adherence to individual HF GDMT classes prior to and following CRT implantation. Results suggested that adherence to HF GDMT classes significantly improved among HF patients after CRT implantation. While an increase in BB adherence would be expected after CRT implantation, an increase in adherence to ACE-I, ARB, and furosemide was also observed.

Results from the analysis of pre- and post-index adherence that showed greater adherence following CRT implantation were robust to differences in the length of the observation periods, HF GDMT classes considered, and analysis of continuous or binary PDC. For example, we saw an increase in adherence to diuretics, as most patients with HF may continue to require diuretic therapy even after implantation with CRT in order to optimize their volume status. However, increased adherence to diuretics is not reflective of a change in dose and does not indicate that the dosage of diuretics increased or changed. Changes in dose of medications pre to post-CRT implantation were outside the scope of this study but may be considered for future research.

Although no gold standard exists for evaluating medication adherence, PDC, evaluated as both a continuous and binary outcome, is one of the most commonly accepted and used measures of adherence, as it more conservatively estimates adherence than other measures (i.e. medical possession ratio)[18,21]. The consistent increase in adherence observed following the index date suggests that either CRT or factors related to CRT, such as decreases in adverse symptom severity, contribute to significantly increasing adherence. Since CRT has been shown to decrease morbidity and mortality of HF patients[6], it is possible that CRT helps achieve greater levels of adherence through its correlation with increased monitoring and receiving higher quality, specialized HF care, which also improve health outcomes and decrease healthcare resource utilization (HRU)[22]. Additional research is needed to better understand the underlying factors resulting in improved adherence observed in patients receiving CRT.

Overall results from the sensitivity analysis, in which patients with cancer and LVAD were not excluded, were very similar to those from the main study population. This sensitivity analysis showed that a prior history of cancer and treatment with oncologic therapies that may be associated with cardiovascular side effects or drug-induced HF do not modify the impact of CRT on adherence. Additionally, the sensitivity analysis of HF medication regimens showed similar results to those of the individual medications: the time trend analysis demonstrates that while adherence showed a slight drop after CRT implantation, the plateau in the months following was higher than that of adherence prior to index. While aldosterone antagonists were considered for this study, they were not included in the analysis because the clinical decision to add them as a medication for patients with chronic systolic HF is based on specific patient indications, symptoms, and clinical judgement as an adjunct to optimal BB, ACE-I and ARB therapy[3].

Other studies have examined the use of GDMT for management of HF after CRT implantation. Witt et al.[23] found that adherence to treatment with HF medications was 95% for BB and 94% for ACE-I/ARB at 4 years following CRT implantation. While these proportions are higher than those

Table 1. Baseline demographics and characteristics of patients in 6-, 12-, and 24- month pre- and post-index periods.

Patient characteristics at baseline[a]	6-Months pre- and post-index $N = 4500$	12-Months pre- and post- index $N = 2603$	24-Months pre- and post- index $N = 829$
Demographic characteristics			
Age, mean ± SD [median]	56.1 ± 7.3 [58.0]	56.0 ± 7.3 [58.0]	56.2 ± 7.1 [58.0]
Female, *n* (%)	1422 (31.6)	847 (32.5)	282 (34.0)
Year of index date			
2008	379 (8.4)	14 (0.5)	0.0 (0.0)
2009	825 (18.3)	525 (20.2)	12 (1.4)
2010	844 (18.8)	567 (21.8)	284 (34.3)
2011	902 (20.0)	635 (24.4)	298 (35.9)
2012	674 (15.0)	451 (17.3)	230 (27.7)
2013	589 (13.1)	407 (15.6)	5 (0.6)
2014	287 (6.4)	4 (0.2)	0.0 (0.0)
Clinical characteristics			
Related cardiovascular conditions			
Any cardiac dysrhythmia[b]	2496 (55.5)	1518 (58.3)	517 (62.4)
Atrial fibrillation and flutter	1330 (29.6)	799 (30.7)	252 (30.4)
Ventricular fibrillation and flutter	195 (4.3)	111 (4.3)	42 (5.1)
Atrioventricular Block	500 (11.1)	317 (12.2)	89 (10.7)
Cardiomyopathy[c]			
Ischemic	1025 (22.8)	631 (24.2)	231 (27.9)
Non-Ischemic	3485 (77.4)	2112 (81.1)	679 (81.9)
Conduction disorders	1916 (42.6)	1220 (46.9)	386 (46.6)
Hypertensive heart disease	286 (6.4)	202 (7.8)	87 (10.5)
Left bundle branch block	1243 (27.6)	801 (30.8)	262 (31.6)
Right bundle branch block	155 (3.4)	110 (4.2)	33 (4.0)
Comorbidities[d]			
Quan-Charlson Comorbidity Index, mean ± SD [median]	2.3 ± 1.6 [2.0]	2.5 ± 1.6 [2.0]	2.6 ± 1.6 [2.0]
Cerebrovascular disease	442 (9.8)	324 (12.4)	129 (15.6)
Chronic kidney disease	426 (9.5)	246 (9.5)	74 (8.9)
Coronary heart disease	1152 (25.6)	719 (27.6)	254 (30.6)
Depression	175 (3.9)	148 (5.7)	56 (6.8)
Diabetes	1617 (35.9)	975 (37.5)	330 (39.8)
Dyslipidemia	2165 (48.1)	1456 (55.9)	525 (63.3)
Hypertension	2548 (56.6)	1687 (64.8)	590 (71.2)
Concomitant medications during pre-index period[e]			
Anticoagulants	1127 (25.0)	709 (27.2)	233 (28.1)
Antiplatelet agents	700 (15.6)	428 (16.4)	141 (17.0)
Calcium channel blockers	431 (9.6)	310 (11.9)	124 (15.0)
Digoxin	915 (20.3)	582 (22.4)	198 (23.9)
Statins	2234 (49.6)	1388 (53.3)	465 (56.1)

Abbreviation. SD, Standard deviation.
[a]*n* (%) were reported for categorical variables; mean ± SD [median] were reported for continuous variables.
[b]Patients may have other types of idysrhythmia than atrial or ventricular fibrillation or flutter (e.g. tachycardia).
[c]It is possible for patients to have both ischemic and non-ischemic cardiomyopathy.
[d]See Quan et al., "Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 Administrative Data." Medical Care, vol. 43, no. 11, Nov. 2005.
[e]Medication use was determined based on the respective claims observed during the pre-index period only.

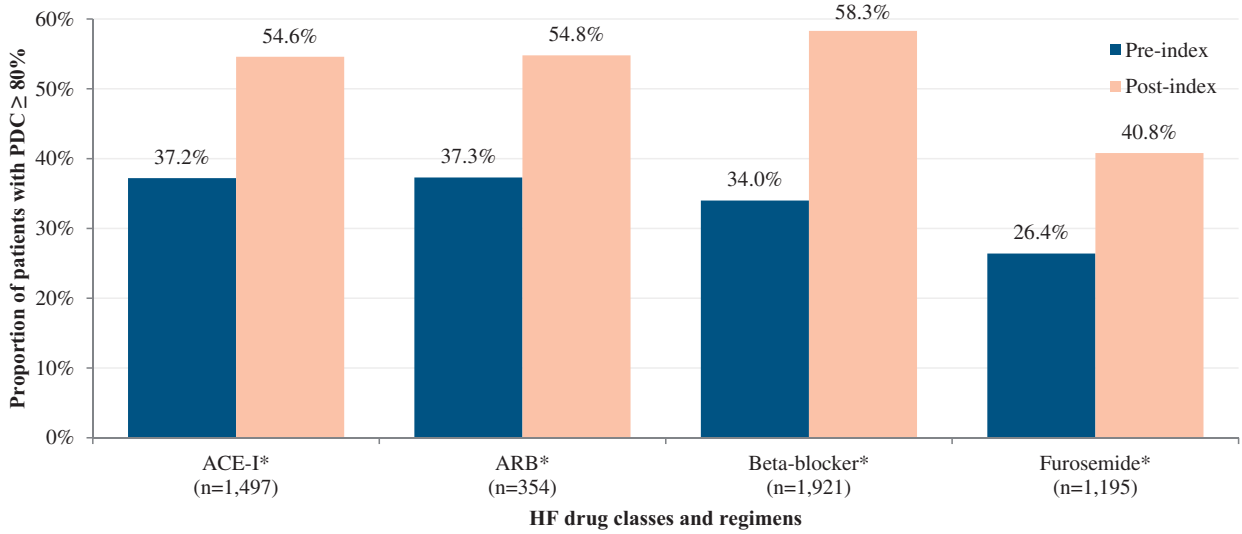

Figure 1. Adherence to HF medication classes for the 12 months pre-index and post-index periods.
*Indicates *p*-value <.05. Abbreviations. ACE-I, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker.

Table 2. Adherence to HF GDMT classes during the pre-index and post-index periods.

	Pre-index	Post-index	Percent change relative to pre-index (%)	*p*-Value[a]
ACE-I				
6-Month pre-index and post-index periods				
Number of patients with ≥1 day on medication for both pre and post, *n*	2423	2423		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.67 ± 0.29 [0.76]	0.75 ± 0.26 [0.86]	11.9	<.001
PDC ≥ 0.80, *n* (%)	1128 (46.6)	1440 (59.4)	27.7	<.001
12-Month pre-index and post-index periods				
Number of patients with ≥1 day on medication for both pre and post, *n*	1497	1497		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.58 ± 0.32 [0.63]	0.71 ± 0.28 [0.83]	22.4	<.001
PDC ≥ 0.80, *n* (%)	557 (37.2)	817 (54.6)	46.7	<.001
24-Month pre-index and post-index periods				
Number of patients with ≥1 day on medication for both pre and post, *n*	517	517		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.48 ± 0.34 [0.43]	0.66 ± 0.30 [0.77]	37.5	<.001
PDC ≥ 0.80, *n* (%)	148 (28.6)	239 (46.2)	61.5	<.001
ARB				
6-Month pre-index and post-index periods				
Number of patients with ≥1 day on medication for both pre and post, *n*	618	618		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.66 ± 0.30 [0.76]	0.75 ± 0.28 [0.88]	13.6	<.001
PDC ≥ 0.80, *n* (%)	290 (46.9)	379 (61.3)	30.7	<.001
12-Month pre-index and post-index periods				
Number of patients with ≥1 day on medication for both pre and post, *n*	354	354		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.59 ± 0.32 [0.64]	0.73 ± 0.27 [0.84]	23.7	<.001
PDC ≥ 0.80, *n* (%)	132 (37.3)	194 (54.8)	47.0	.006
24-Month pre-index and post-index periods				
Number of patients with ≥1 day on medication for both pre and post, *n*	104	104		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.47 ± 0.33 [0.38]	0.65 ± 0.31 [0.77]	38.3	<.001
PDC ≥ 0.80, *n* (%)	26 (25.0)	42 (40.4)	61.5	.003
BB				
6-Month pre-index and post-index periods				
Number of patients with ≥1 day on medication for both pre and post, *n*	3224	3224		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.67 ± 0.29 [0.74]	0.77 ± 0.24 [0.87]	14.9	<.001
PDC ≥ 0.80, *n* (%)	1422 (44.1)	1992 (61.8)	40.1	<.001
12-Month pre-index and post-index periods				
Number of patients with ≥1 day on medication for both pre and post, *n*	1921	1921		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.57 ± 0.31 [0.60]	0.75 ± 0.25 [0.85]	31.6	<.001
PDC ≥ 0.80, *n* (%)	653 (34.0)	1119 (58.3)	71.4	<.001
24-Month pre-index and post-index periods				
Number of patients with ≥ 1 day on medication for both pre and post, *n*	632	632		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.47 ± 0.33 [0.41]	0.72 ± 0.26 [0.82]	53.2	<.001
PDC ≥ 0.80, *n* (%)	162 (25.6)	337 (53.3)	108.0	<.001
Furosemide				
6-Month pre-index and post-index periods				
Number of patients with ≥1 day on medication for both pre and post, *n*	1986	1986		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.60 ± 0.30 [0.63]	0.70 ± 0.28 [0.79]	16.7	<.001
PDC ≥ 0.80, *n* (%)	685 (34.5)	970 (48.8)	41.6	<.001
12-Month pre-index and post-index periods				
Number of patients with ≥ 1 day on medication for both pre and post, *n*	1195	1195		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.50 ± 0.32 [0.44]	0.64 ± 0.29 [0.71]	28.0	<.001
PDC ≥ 0.80, *n* (%)	316 (26.4)	488 (40.8)	54.4	<.001
24-Month pre-index and post-index periods				
Number of patients with ≥ 1 day on medication for both pre and post, *n*	398	398		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.38 ± 0.32 [0.24]	0.57 ± 0.31 [0.60]	50.0	<.001
PDC ≥ 0.80, *n* (%)	76 (19.1)	122 (30.7)	60.5	.003

Abbreviations. AA, aldosterone antagonists; ACE-I, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BB: Beta-blocker; DRI, Direct renin inhibitors; PDC, Proportion of days covered; SD, Standard deviation.

[a]Comparisons of adherence between pre-index and post-index periods were conducted for paired data using the Wilcoxon sign-rank test for continuous variables and McNemar's test for categorical variables.

[b]Proportion of days covered (PDC) was calculated as the sum of the number of unique days during which the patient had all medications on hand, divided by a fixed time interval of either 6, 12, or 24 months as applicable.

found in our study, the definition of adherence that Witt et al. used (i.e. "continued treatment during follow-up in patients receiving an HF medication 6 months after implantation") is different than the more commonly accepted metric of PDC used in our study, which typically measure the extent to which a patient is compliant to their medication. "Continued treatment" is not easily comparable to PDC or MPR. Thus, it is not surprising for the proportions reported by Witt et al. to be higher than those we found given the more stringent measured used in this study.

The results of this study should be interpreted in light of some limitations. First, findings of this study are based on a retrospective analysis of claims data and, therefore rely on the accuracy of information in medical and drug claims in this database. Second, adherence was measured according to the number of days of possible medication coverage, as reflected by days of supply in pharmacy claims, and thus may be overestimated; whether or not all medication supplied to the patient is actually used as directed is unknown. This adherence calculation did, however, use PDC, a widely accepted measurement and a more conservative estimate of adherence than alternatives (i.e., medical possession ratio), which should help mitigate this limitation[18,24]. Third, the study was limited to patients aged 18 to 64 years of age, as patients aged 65 years or older are eligible for prescription drug coverage through Medicare Part D plans. As a result, their prescription drug claims would not be included in the MarketScan database, which only captures claims from commercial insurance plans, such as employer-sponsored retiree Medicare Supplemental plans. Missing drug claims for these patients would have impacted our assessment of adherence and thus biased study results. Due to the exclusion of these older patients, study results are not generalizable to all HF (or CRT) patients, many of whom are aged 65 years or older. Fourth, the study lacked a control group of patients without CRT to compare with patients with CRT with respect to adherence. Hence, it is difficult to distinguish the effect of CRT on adherence from possible secular changes in clinical practice, or other changes pertaining to the patient's health condition (e.g. disease progression) over time. To address this issue, monthly PDC was plotted in order to observe the impact of granular changes in PDC over time. Fifth, prescribing patterns are not always reflective of GDMT in individual patients, therefore the generalizability of results to a larger HF-patient population is limited[25]. Finally, the claims database that we used does not include information about contraindications or patients reasons for initiating and/or discontinuing certain therapies. Despite these limitations, the real-world approach used in this study of thousands of patients is appropriate for studying the impact of CRT implantation on patient medication adherence and has been applied and tested across multiple chronic medication classes (and regimens) to produce accurate assessments of medication adherence in patient populations[18].

Conclusion

The findings from our study are important to real-world practice as they demonstrate that CRT implantation is associated with improved adherence to GDMT therapy, which is critical for the management of HF and reductions in HF-related HRU, morbidity, and mortality. To date, clinical trials have only assessed the impact of CRT implantation on clinical outcomes, hospitalization rates, and HF clinical composite responses[6,9]. This study is one of the first to assess the impact of a medical device such as CRT implantation on adherence to GDMT. Although the underlying mechanisms driving results from this study may be numerous, the findings of this study suggested a positive effect of CRT implantation on patients' adherence to HF GDMT classes. Future studies should explore the factors associated with the improvement of adherence observed in the current analysis.

Transparency

Declaration of funding

This study was supported by Medtronic, Mounds View, MN

Declaration of financial/other relationships

MD, ED, PL, and MSD are employees of Analysis Group Inc., which receives grant/research support from Medtronic Inc.; YX and DK were employees of Analysis Group Inc. when this research was conducted; ST, DM, and XL are employees of Medtronic Inc. and report receiving a salary and stock options; JD and BS received consulting fees from Medtronic Inc. for their participation in this study. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work but have no other relevant financial relationships to disclose.

Author contributions

All authors were involved in the conception and design, or analysis and interpretation of the data; the drafting of the paper or revising it critically for intellectual content; and the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Previous presentations

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Appendix

Table A1. Adherence to HF medication regimens during the pre-index and post-index periods.

	Pre-index	Post-index	Percent change relative to pre-index (%)	*p*-Value[a]
	Medication regimen 1 (ACE-I/ARB/DRI + BB)			
6-Month pre-index and post-index periods				
Number of patients with ≥1 day on regimen for both pre and post, *n*	2597	2597		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.59 ± 0.29 [0.62]	0.67 ± 0.27 [0.76]	14.8	<.001
PDC ≥ 0.80, *n* (%)	824 (31.7)	1178 (45.4)	43.0	<.001
12-Month pre-index and post-index periods				
Number of patients with ≥1 day on regimen for both pre and post, *n*	1602	1602		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.49 ± 0.30 [0.44]	0.64 ± 0.28 [0.72]	31.9	<.001
PDC ≥ 0.80, *n* (%)	371 (23.2)	639 (39.9)	72.2	<.001
24-Month pre-index and post-index periods				
Number of patients with ≥1 day on regimen for both pre and post, *n*	540	540		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.38 ± 0.30 [0.29]	0.60 ± 0.29 [0.67]	57.5	<.001
PDC ≥ 0.80, *n* (%)	88 (16.3)	178 (33.0)	102.3	<.001
	Medication regimen 2 (ACE-I/ARB/DRI + BB + Furosemide)			
6-Month pre-index and post-index periods				
Number of patients with ≥1 day on regimen for both pre and post, *n*	1375	1375		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.48 ± 0.29 [0.46]	0.55 ± 0.29 [0.57]	16.2	<.001
PDC ≥ 0.80, *n* (%)	266 (19.3)	379 (27.6)	42.5	<.001
12-Month pre-index and post-index periods				
Number of patients with ≥1 day on regimen for both pre and post, *n*	860	860		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.38 ± 0.29 [0.30]	0.50 ± 0.30 [0.51]	30.7	<.001
PDC ≥ 0.80, *n* (%)	117 (13.6)	179 (20.8)	53.0	<.001
24-Month pre-index and post-index periods				
Number of patients with ≥1 day on regimen for both pre and post, *n*	298	298		
Proportion of days covered[b]				
PDC, mean ± SD [median]	0.27 ± 0.27 [0.15]	0.43 ± 0.29 [0.41]	59.5	<.001
PDC ≥ 0.80, *n* (%)	22 (7.4)	43 (14.4)	95.5	.003

Abbreviations. ACE-I, angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BB, Beta blocker; DRI, Direct renin inhibitors; PDC, Proportion of days covered; SD, Standard deviation.

[a]Comparisons of adherence between pre-index and post-index periods were conducted for paired data using the Wilcoxon sign-rank test for continuous variables and McNemar's test for categorical variables.

[b]Proportion of days covered (PDC) was calculated as the sum of the number of unique days during which the patient had all medications in the regimen on hand, divided by a fixed time interval of either 6, 12, or 24 months as applicable.

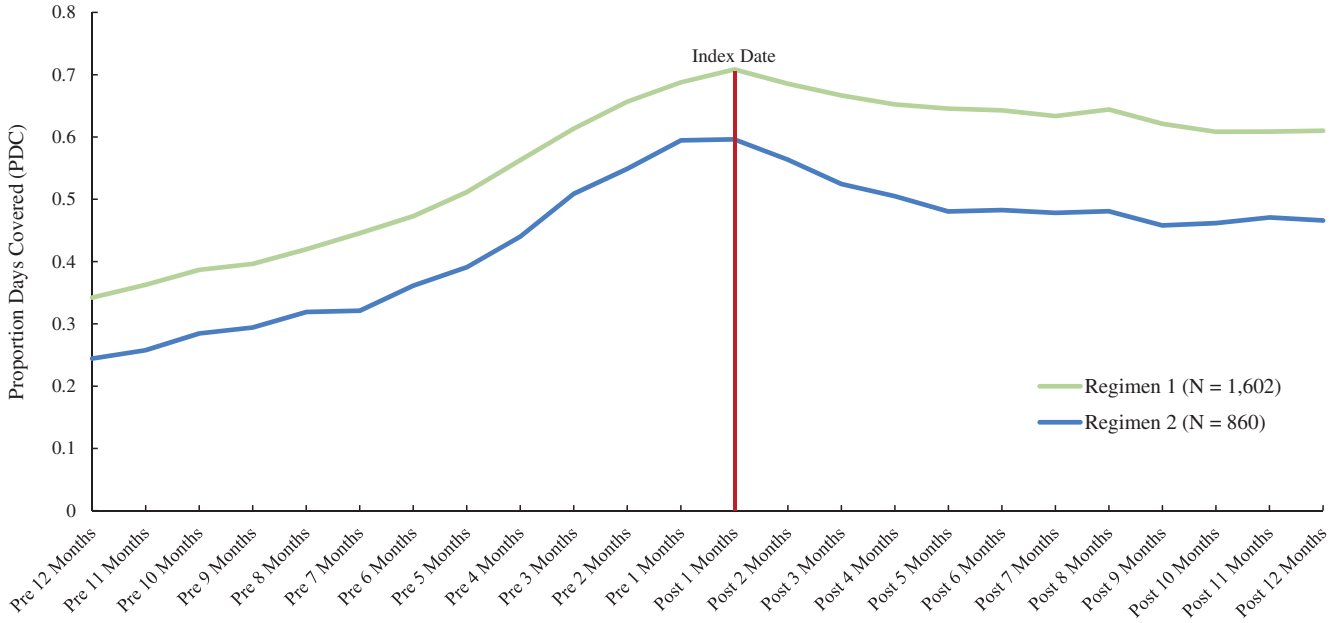

Figure A1. Adherence to medication regimens 1 and 2 during the 12 months pre- and post-CRT implantation. On an average, mean PDC was lower for regimens 1 and 2 over the total course of the 12 months pre- versus 12-months post-CRT implantation. Though an increasing trend in PDC is observed leading up to CRT implantation and a slight decrease in PDC is observed following this point, PDC is observed to remain higher than observed pre-index levels (seen $\geq$3–4 months prior to CRT implantation) through the end of the post-CRT 12-month period.