Temporal Trends in Adherence to Cardiovascular Medications in Elderly Patients After Hospitalization for Heart Failure

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Although the complexity of treatment regimens for patients with heart failure (HF) has increased over time because of the increased availability of efficacious medications, little is known about temporal trends in adherence to treatment regimens in these patients. We assessed trends in adherence to angiotensin-system blockers (ABs), β-blockers (BBs), and spironolactone (SL) for HF in Medicare beneficiaries enrolled in two statewide pharmacy benefit programs from 1995 to 2004. The proportion of days covered (PDC) (%) was assessed after the first dispensing among users of an AB, BB, or SL. Proportions of full adherence (PDC >80%) did not change over time for ABs (54% in both 1996 and 2003) but increased slightly for BBs (from 47% in 1996 to 57% in 2003) and SL (from 31% in 1996 to 42% in 2003). Black race and dialysis treatment predicted poor adherence to any medications. Adherence to BBs and SL increased modestly over time, but overall nonadherence remained high.

Nonadherence to medication regimens is a common problem among patients with heart failure (HF), and it limits the potential benefit offered by these drugs. Studies estimate that 30–60% of patients with HF do not take medications as prescribed.[1,2] In fact, nonadherence is suggested to be the most common cause of preventable rehospitalizations.[3] Several trials have demonstrated the benefit of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), β-blockers (BBs), and spironolactone (SL) in reducing rehospitalizations and mortality in patients with HF due to systolic dysfunction.[4,5] As a result, standard drug regimens for HF have become more complex. The average number of daily medications for a Medicare HF patient increased from 6.8 during the period 1998–1999 to 7.5 during 2000–2001.[6] On the other hand, various approaches have been employed and tested to improve adherence in patients with HF and other chronic cardiovascular diseases.[7–10] However, little is known about temporal trends in adherence to these cardiovascular medications among elderly US patients with HF. We assessed trends in adherence to angiotensin-system blockers (ABs), including ACEIs and ARBs, BBs, and SL prescribed for HF in Medicare beneficiaries enrolled in two statewide pharmacy benefit programs (1995–2004).

RESULTS

Study patients

We identified 54,153 patients who had undergone at least one hospital admission for HF between 1 January 1995 and 31 December 2003, had been active participants in their insurance programs for >1 year prior to the index HF admission, and had undergone no nursing home admission either in the 365 days before or within 90 days after the index HF hospitalization. Of these, the 46,278 (85.5%) who survived ≥90 days after discharge constituted the final study cohort. The characteristics of these patients are shown in **Table 1**. The patients had a mean age of 80 years, 72% were female, and 9% were black. Several comorbid conditions were quite common: 7% had experienced a myocardial infarction in the year prior to the index date, 69% had previously been diagnosed with coronary artery disease, 65% had been diagnosed with HF, 29% had cerebrovascular disease, 70% had hypertension, 47% had diabetes, 48% had chronic pulmonary disease, and 19% had been diagnosed with chronic kidney disease (**Table 1**).

Adherence to medication regimen after hospitalization for HF

Of 46,278 HF patients, 49, 29, and 5% filled prescriptions for ABs, BBs, and SL, respectively, within 90 days after HF hospital

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Table 1 Baseline characteristics of study cohort

	1995	1996	1997	1998	1999	2000	2001	2002	2003	All years
Total population, *n*	7,619	7,012	6,033	5,023	4,516	4,187	3,949	3,993	3,946	46,278
Follow-up, years	2.8 (4.2)	3.8 (4.6)	3.1 (4.5)	3.2 (4.5)	3.5 (3.8)	3.4 (2.9)	3.1 (2.0)	2.2 (1.1)	1.4 (0.6)	2.6 (3.2)
Age, years	80 (11)	80 (11)	80 (11)	80 (11)	80 (11)	80 (11)	81 (11)	80 (11)	80 (11)	80 (10)
Male	27	27	28	28	27	27	27	29	30	28
Race (black)	8	9	9	9	10	9	9	10	10	9
Health-service use										
Number of physician visits	10 (9)	9 (9)	10 (9)	10 (9)	9 (9)	10 (9)	10 (9)	10 (10)	10 (10)	10 (9)
Number of medications	10 (8)	9 (8)	10 (9)	9 (9)	10 (10)	10 (10)	10 (10)	11 (10)	11 (9)	10 (9)
Charlson comorbidity scores	3 (3)	3 (2)	3 (2)	3 (2)	3 (2)	3 (3)	3 (3)	3 (3)	3 (3)	3 (3)
Recent acute-care hospitalization	60	50	50	48	49	48	48	49	49	51
Length of stay for the index HF	7(4)	6 (4)	6 (5)	6 (4)	6 (4)	6 (4)	5 (4)	5 (4)	5 (4)	6 (4)
Previous diagnosis										
Coronary artery disease	71	69	68	68	69	68	69	68	70	69
Recent MI (365 days)	8	8	7	7	7	7	7	6	7	7
Atrial fibrillation	43	45	45	43	45	46	48	47	48	45
Hypertension	62	63	66	68	71	73	78	79	82	70
Cerebrovascular disease	27	27	28	30	30	29	31	30	33	29
Prior diagnosis of heart failure	70	65	64	63	63	64	63	64	64	65
Diabetes	45	45	45	45	46	49	50	51	51	47
Chronic pulmonary disease	49	46	48	47	48	49	49	50	50	48
Chronic kidney disease	18	16	16	16	18	19	20	23	25	19
Dialysis	2	2	2	2	2	2	3	3	3	2
Osteoarthritis	34	33	35	36	37	38	39	41	40	36
Cancer	20	21	21	22	21	23	22	23	23	21
Gastrointestinal bleeding	7	5	5	5	5	6	5	5	5	6
Dementia	8	8	10	11	11	12	12	12	13	10
Depression	14	13	15	15	17	17	18	19	21	16
Obesity	5	6	6	6	8	7	8	9	9	7
Use of drugs prior to the HF hospitalization										
β-Blockers	20	21	24	26	31	33	37	44	48	30
Angiotensin-system blockers	45	41	38	39	39	39	40	45	46	41
Calcium channel blockers	46	43	41	38	39	36	35	37	35	40
Spironolactone	2	2	2	2	2	4	5	5	6	3
Statins	7	8	12	16	19	22	27	32	34	18
Loop diuretics	44	46	46	43	46	49	49	52	54	47
Warfarin	20	19	19	19	20	19	21	22	24	20
Digoxin	21	26	29	29	27	27	26	25	23	26

Values represent % for categorical variables and median (interquartile range) for continuous variables. Covariates were assessed during the 12-month period prior to and during the index MI admission.

HF, heart failure; MI, myocardial infarction.

discharge. Among those who filled prescriptions, the overall adherence to the study medication regimens was low (55.9% for ABs, 54.5% for BBs, and 37.6% for SL). Whereas modest increases in adherence over time were observed for BBs (45.6% in 1996 and 57.3% in 2003) and SL (31.0% in 1996 and 41.5% in 2003), no significant changes were seen for ABs (53.1% in 1996 and 54.4% in 2003; **Figure 1**). In a multivariate model, after adjusting for patient demographics, comorbidity, medication, and procedure use, and considering calendar year as a continuous variable, there were significant trends toward greater adherence with respect to both BBs (2%, 95% confidence interval (CI): 1–3% per year) and SL (3%, 95% CI: 1–6% per year). When each calendar year was treated as a separate individual variable in the multivariate model (without assuming a linear relationship

Table 2 Multivariable predictors of the odds of being fully adherent (PDC ≥80%)

	Angiotensin-system blockers				β-Blockers				Spironolactone			
Model covariate	RR	95% CI		*P* value	RR	95% CI		*P* value	RR	95% CI		*P* value
Year 1995	Ref.				Ref.				Ref.			
Year 1996	1.01	0.97	1.06	0.521	1.09	1.00	1.19	0.039	1.07	0.77	1.50	0.676
Year 1997	1.06	1.02	1.11	0.004	1.10	1.01	1.20	0.021	0.73	0.48	1.10	0.133
Year 1998	1.09	1.05	1.14	<0.0001	1.20	1.11	1.30	<0.0001	1.00	0.68	1.48	0.989
Year 1999	1.07	1.02	1.13	0.003	1.14	1.05	1.23	0.002	1.29	0.96	1.72	0.088
Year 2000	1.00	0.95	1.05	0.978	1.23	1.14	1.33	<0.0001	1.38	1.05	1.83	0.022
Year 2001	1.02	0.97	1.08	0.413	1.18	1.09	1.28	<0.0001	1.17	0.87	1.55	0.296
Year 2002	1.02	0.97	1.07	0.524	1.20	1.11	1.29	<0.0001	1.16	0.87	1.55	0.307
Year 2003	0.98	0.93	1.03	0.499	1.22	1.13	1.32	<0.0001	1.34	1.01	1.76	0.042
Black	0.77	0.73	0.81	<0.0001	0.73	0.67	0.78	<0.0001	0.79	0.60	1.03	0.087
Age (by 10 years)	1.02	1.00	1.04	0.0175	1.02	1.00	1.05	0.099	1.05	0.97	1.15	0.214
Male	0.91	0.88	0.94	<0.0001	0.91	0.87	0.94	<0.0001	0.90	0.79	1.01	0.077
Prior heart failure hospitalization	0.95	0.92	0.97	0.000	0.92	0.88	0.95	<0.0001	0.92	0.80	1.06	0.253
Chronic pulmonary disease	1.00	0.98	1.03	0.991	0.98	0.95	1.01	0.269	0.96	0.86	1.08	0.516
Dementia	0.99	0.94	1.03	0.554	0.95	0.90	1.01	0.116	0.99	0.83	1.18	0.894
Hypertension	1.02	1.00	1.05	0.108	1.04	1.00	1.08	0.049	0.93	0.83	1.06	0.281
Chronic kidney disease	0.91	0.88	0.94	<0.0001	0.99	0.95	1.03	0.714	0.94	0.82	1.08	0.389
Dialysis	0.78	0.68	0.89	0.000	0.79	0.69	0.91	0.001	1.67	0.89	3.16	0.111
Peripheral vascular disease	1.00	0.97	1.03	0.924	0.96	0.93	1.00	0.050	0.94	0.83	1.07	0.331
Diabetes	1.03	1.00	1.06	0.040	1.03	0.99	1.06	0.147	0.98	0.87	1.11	0.764
Number of physician visits	1.00	1.00	1.00	0.901	1.00	1.00	1.00	0.117	0.99	0.98	0.99	0.000
Prior hospitalization	0.95	0.92	0.98	0.001	0.95	0.91	0.99	0.007	0.97	0.86	1.10	0.636
Length of stay	1.00	1.00	1.00	0.585	1.00	1.00	1.01	0.027	0.99	0.98	1.01	0.414
Prior warfarin use	1.07	1.04	1.10	<0.0001	1.04	1.00	1.08	0.077	1.17	1.04	1.33	0.012
Prior angiotensin blocker use	1.12	1.09	1.15	<0.0001	1.03	1.00	1.07	0.060	0.95	0.85	1.06	0.329
Prior β-blocker use	1.05	1.02	1.08	0.000	1.13	1.09	1.17	<0.0001	1.02	0.91	1.14	0.735
Prior calcium channel blocker use	1.05	1.02	1.08	<0.0001	1.02	0.99	1.05	0.214	1.17	1.05	1.30	0.006
Spironolactone	0.91	0.84	0.98	0.012	0.96	0.88	1.04	0.296	1.11	0.99	1.25	0.080

The final multivariate models for predictors of adherence included all variables in **Table 1**. Only subsets of variables in the models are shown in **Table 2**.

CI, confidence interval; PDC, proportion of days covered; RR, risk ratio.

between the level of adherence and calendar year), the increases in adherence from 1995 to 2003 were 22% (95% CI: 13–32%) for BBs and 34% (95% CI: 1–76%) for SL.

Patient-related predictors of adherence

Table 2 lists multivariate predictors of adherence. Black race, male gender, history of HF, hospitalization for any reason, and being a recipient of dialysis treatment predicted poor adherence to AB and BB regimens. Black race and male gender tended to be associated with poor adherence to SL, but the association was only marginally significant. The use of the same drug class prior to the index hospitalization was associated with better adherence with respect to ABs and BBs but not to SL. Overall, c-statistics (a measure of discrimination for a prediction model) of our logistic regression models predicting adherence to the study medications ranged from 0.59 to 0.62, indicating that only a small proportion of the variability in adherence was explained by these patient-related factors.

Sensitivity analyses in subgroups

Trends in adherence to ABs, BBs, and SL among patients with new-onset HF, among new users of the study medications, and among those who appeared to have experienced HF due to systolic dysfunction are shown in **Figure 2**. Despite some differences in the actual frequencies of adherence, the general trends in adherence to study medications in all the subgroups were similar to those in the overall study population.

DISCUSSION

Our analysis of Medicare beneficiaries enrolled in two state pharmacy assistance programs demonstrates modest increases over time in adherence to BB and SL, but not to AB, among patients who had undergone hospitalization for HF. Despite these improvements, overall nonadherence rates have remained high.

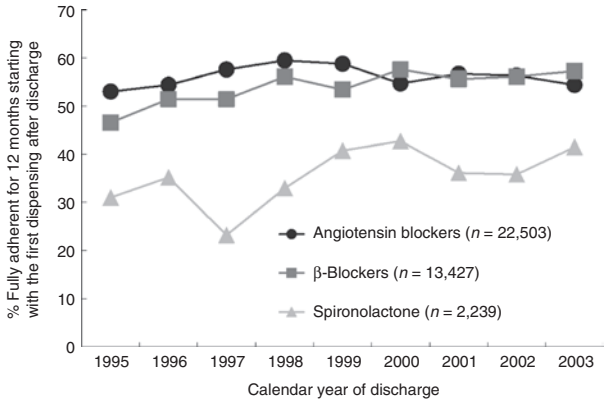

Figure 1 Time trends during 1995–2003 in adherence to angiotensin blockers, β-blockers, and spironolactone in patients with heart failure.

Masoudi *et al.* showed that, in elderly patients with HF, the prescription of an ACEI at discharge was associated with a 14% reduction in 1-year mortality among those who survived hospitalization for HF.[11] Johnson *et al.* demonstrated that Canadian senior citizens who had been hospitalized for new HF and filled a prescription for ABs and/or BBs within 3 months of discharge had a 1-year mortality of 16.6% as compared with 29.9% in those with no prescription for either class of drug.[12] However, the benefits of being prescribed ABs and BBs may not have been fully realized if patients did not adhere to these medications. In fact, nonadherence is suggested to be the most common cause of preventable rehospitalizations in HF patients.[3] Our analysis demonstrates that first-year adherence to cardiovascular HF medications is poor among elderly patients, ranging from 35 to 55%.

Previous studies assessing adherence to cardiovascular medications in HF used various methods to define adherence in different settings. A study using pill counts and electronic pill caps suggested that ~30% of general HF patients do not take their medications as prescribed.[1] This study also estimated nonadherence to medication regimens among disadvantaged subgroups to be ~60%. The low to modest adherence rates observed in our study, using longitudinal dispensing data, fall within the range of estimated medication adherence in previous studies.[13–15] Butler *et al.* assessed the proportion of patients who filled prescriptions of ACEI in 30 days and/or subsequently—up to 365 days after discharge in a Medicaid population. Among 960 HF patients, only 63.3% were still using an ACEI after 365 days.[14] In another

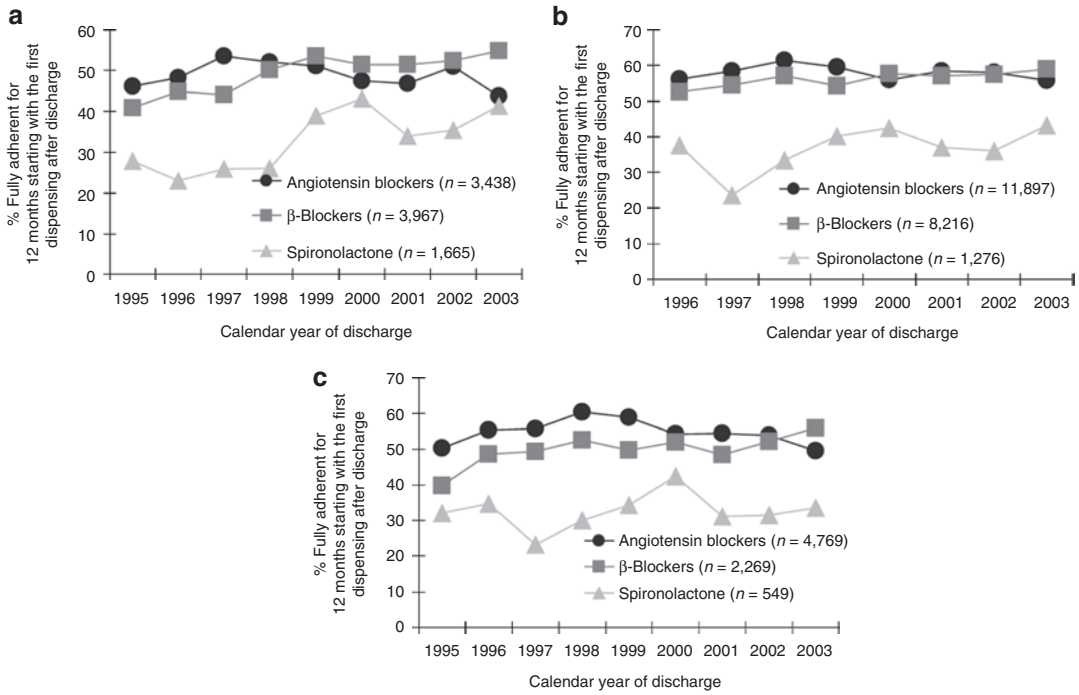

Figure 2 Time trends during 1995–2003 in adherence to angiotensin blockers, β-blockers, and spironolactone in subgroups of patients with heart failure. (**a**) New users of study medications; (**b**) new-onset heart failure; and (**c**) presumed systolic dysfunction.

Medicaid population, Monane *et al*. estimated adherence to digoxin in patients with HF. They found that only 10% filled enough prescriptions to have sufficient supply for the year of study.[13] Self-reported adherence to ACEI in patients with coronary artery disease and HF in 1995–2002 was 39% (ref. 15). Our study was the first to formally assess temporal trends in adherence to ACEIs, BBs, and SL; unfortunately, we were unable to find any evidence of major improvements.

As indicated by the low c-statistics of the model predicting adherence, patient characteristics including comorbidity and use of health services or medications have little appreciable effect on adherence. However, there are many other potential reasons for the observed low levels of adherence, including the complexity of treatment regimens, side effects, cognitive impairment, poor understanding of the benefits of treatment, poor provider–patient relationships, and difficulty in accessing physicians and pharmacies.[8] Despite the proven benefits in survival, patients often do not experience improvements in their symptoms after taking these medications, and ensuring adherence to medication regimens may therefore be particularly challenging. Also, patients with advanced HF often have low blood pressure and may not tolerate multiple antihypertensive medications. This might also explain the modest—if any—improvement in the trends of adherence. In a small but detailed study assessing the reasons for nonadherence in HF patients, Mockler *et al*. showed that, of the instances of medications being discontinued by patients, 50% involved no medical cause, 30% were attributable to adverse drug reactions, and 15% were for a justified medical reason.[16]

Our analysis identified several predictors of adherence, including age, gender, race, and prior hospitalization, some of which have been demonstrated in other studies to influence rates of adherence.[17] Comorbid conditions, such as end-stage renal disease requiring dialysis, were associated with lower rates of adherence to treatment for HF; this may reflect reluctance on the part of physicians or patients to continue recommended medications for secondary prevention, in consideration of the poor prognosis of the primary condition. The presence of chronic kidney disease increases the risk of hyperkalemia and of increases in creatinine levels, which may limit the ability of these patients to remain on ABs or SL. It is worth noting that the results of previous studies on the effect of these factors are not consistent, probably because of the great heterogeneity in the assessment methods, in the definition of "adherence," and in study populations.

Our study has several limitations. First, we conducted our analysis using data from state pharmacy assistance programs in two US states that provide prescription drug benefits to low- to middle-income patients ≥age 65. Our cohort consisted of older, predominantly female, patients with a high prevalence of comorbid conditions, and the results may not be generalizable to younger and/or more affluent groups. Second, our data do not contain detailed clinical information that may explain the causes for discontinuation of medications. Therefore, it is possible that patients discontinued the prescribed medications for clinically appropriate reasons such as hyperkalemia associated with the use of ACEI, ARB, or SL. Nonetheless, this limitation is likely to apply nondifferentially across all calendar years and therefore will not affect the interpretation of the time trend. Finally, because of the lack of detailed clinical information, we were unable to determine whether these patients had HF due to systolic dysfunction or HF with preserved ejection fraction. However, we assessed adherence only in those who were started on the study medications. We also conducted sensitivity analyses among those who might have systolic dysfunction by identifying subjects who were on digoxin but did not have diagnoses of atrial fibrillation; this did not change the outcome meaningfully.

Our study provides important information on the recent time trends and the magnitude of the problem with respect to nonadherence in elderly patients with HF. Because of the health and economic consequences of nonadherence, an understanding of the modifiable reasons for suboptimal adherence and the development of effective strategies to improve medication adherence, along with rigorous evaluations to understand the effectiveness and cost-effectiveness of existing interventions, will help practitioners and policy makers to optimize the care of elderly patients with HF.

METHODS

Data sources and study population. We linked medical claims data for the years 1994–2005 from several sources, namely, programs of the New Jersey Medicare and Pharmaceutical Assistance for the Aged and Disabled (PAAD) and the Pennsylvania Medicare and Pharmaceutical Assistance Contract for the Elderly (PACE). These programs provide comprehensive prescription drug coverage for eligible elderly patients in New Jersey and Pennsylvania. Patients are eligible if their income is above the Medicaid annual income threshold but less than approximately $35,000. Neither program restricts the use of any HF medication with prior authorization requirements.

We identified the first hospitalization for HF in the study population during the period 1 January 1995 to 31 December 2003, indicated by an ICD (International Classification of Disease, 9th revision) code of 428 as the primary discharge diagnosis. This definition has previously been validated and shown to have a positive predictive value of 94% (ref. 18). We accepted only patients who survived up to the time of filling at least one prescription for an AB (ACEI or ARB), BB, or SL within 90 days of hospital discharge. We excluded patients who were admitted to a nursing home within 90 days after discharge from the index HF hospitalization date, so as to ensure complete assessment of medication use. The date of the first dispensing for a study drug was considered the index date in our analysis. Commencing from the index date, the data were censored at the earliest of the following time points: date of death, date of nursing home entry, or 1 year from index date. All patients were required to have had at least one filled prescription and at least one claim for a clinical service during each of the two consecutive 6-month periods prior to the index HF hospitalization, so as to ensure their ongoing eligibility and the uniform assessment of prior comorbid conditions. All traceable person-specific identifying factors were transformed into anonymous, coded study numbers to protect subjects' privacy. The institutional review board of Brigham and Women's Hospital approved this study.

Assessment of adherence. Among patients who received one or more of the drugs belonging to the relevant drug classes after the index hospitalization for HF, we evaluated medication adherence by determining the proportion of days covered (PDC) for each medication, which is a valid and widely used adherence metric.[19] Adherence generally refers to whether a patient takes medications as prescribed, whereas persistence generally indicates whether a patient stays on medications. It may be of importance to note that our data have limited validity in assessing the persistence, that is, the proportion of patients who continued to take the

medications for the entire year vs. those who stopped taking them in the relevant period. This is because our data do not completely capture pharmacy records after patients enter a nursing home.

The PDC is calculated by dividing the number of days of medication supplied (numerator) by the number of days (denominator) in a given interval. In our analysis, the numerator was the sum of the number of days for which medication was supplied on each prescription after the first dispensing, up to 1 year after the index date or the occurrence of any of the censoring events, whichever was earlier. The denominator was the number of days between the index date and either the censoring date or 1 year after the index date, whichever was earlier. In this manner, censoring because of the death or nursing home entry of a patient was adequately accounted for in our calculation of PDC. For dispensings filled near the end of the observation period, we counted only the days supplied up to the end of the observation period. The number of days during which patients were hospitalized after the index date was subtracted from the denominator. We considered all drugs within a given therapeutic class to be interchangeable. On the basis of their calculated PDCs, we classified patients into one of three groups using standard thresholds: ≥80% ("fully adherent"), 40–80% ("partially adherent"), and <40% ("nonadherent").[20]

Covariates. From enrollment files, we obtained information on age (on the date of index HF hospitalization), gender, and race (Black, White, or other) of the patients. We also assessed for the presence of several comorbid conditions, including indications and contraindications for the study drugs, using each patient's inpatient and outpatient claims history for the 12-month period preceding the discharge date from the index hospitalization. These comorbid conditions included hypertension, coronary artery disease, myocardial infarction, prior HF,[18] cerebrovascular disease,[21] peripheral vascular disease,[21] atrial fibrillation,[22] arthritis,[23] diabetes, chronic kidney disease,[24] maintenance dialysis, chronic pulmonary diseases, liver diseases, gastrointestinal bleeding or ulcer,[25] alcohol abuse, dementia, depression, any malignancy except nonmelanoma skin cancer, HIV infection, and obesity. The characteristics of the index hospitalization, such as the length of stay, were also recorded. For each patient, health-care utilization indicators were also measured for the year preceding the HF admission. These included number of hospital days, physician visits, prescriptions for different drugs filled, and nursing home stay. We also assessed each patient's previous uses of one or more of a variety of cardiovascular drugs, including the study drugs (ABs, BBs, SL), loop diuretics, statins, warfarin, and digoxin (see **Table 1**).

Statistical analysis. We assessed whether the proportion of patients who were "fully adherent" to therapy (i.e., PDC ≥80%) changed over time, by plotting the frequency of change using 1-year intervals. We used multivariate modified Poisson regression models to assess the trend over time after adjusting for the covariates described in **Table 1**. Unlike logistic regression, modified Poisson regression allows direct estimation of risk ratios and the corresponding 95% CIs when the outcome cannot be considered rare.[26] As subgroup analyses, we repeated the same set of analyses among (i) patients with new-onset HF (i.e., no prior HF hospitalizations during the 2 years prior to the first HF hospitalization identified during the study period), (ii) new users (i.e., patients who had not been dispensed the study drug during the 1 year prior to the index date), and (iii) patients who were considered more likely to have HF due to systolic dysfunction. The latter were identified by the presence of at least one prescription for digoxin during the 90 days after the discharge from the index HF hospitalization; however, data from these patients were not considered if they had been diagnosed with atrial fibrillation at any time during the 365 days prior to and during the index hospitalization. This definition had a positive predictive value of 84% for identifying patients with ejection fraction <45% among 1,072 Medicare PAAD/PACE patients who had a quantitative assessment of ejection fraction during the hospitalization per the records in a national HF/myocardial infarction registry.[27] The statistical significance of regression coefficients in all our models was assessed using two-sided tests. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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