

Effectiveness of β -Blockers in Heart Failure With Left Ventricular Systolic Dysfunction and Chronic Kidney Disease

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ABSTRACT

Background: Establishing medication effectiveness outside of a randomized trial requires careful study design to mitigate selection bias. Previous observational studies of β -blockers in patients with chronic kidney disease and heart failure have had methodologic limitations that may have introduced bias. We examined whether initiation of β -blocker therapy was associated with better outcomes among patients with chronic kidney disease and newly diagnosed heart failure with left ventricular systolic dysfunction.

Methods and Results: We identified 668 adults in the Kaiser Permanente Northern California system from 2006 to 2008 with chronic kidney disease, incident heart failure, left ventricular systolic dysfunction, and no previous β -blocker use. We defined chronic kidney disease as estimated glomerular filtration rate $<60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ or proteinuria, and we excluded patients receiving dialysis. We used extended Cox regression to assess the association of treatment with death and the combined end point of death or heart failure hospitalization. Initiation of β -blocker therapy was associated with a significantly lower crude risk of death (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.35–0.63), but this association was attenuated and no longer significant after multivariable adjustment (HR 0.75, CI 0.51–1.12). β -Blocker therapy was significantly associated with a lower risk of death or heart failure hospitalization even after adjustment for potential confounders (HR 0.67, CI 0.51–0.88).

Conclusions: β -Blocker therapy is associated with lower risk of death or heart failure hospitalization among patients with chronic kidney disease, incident heart failure, and left ventricular systolic dysfunction. (*J Cardiac Fail* 2013;19:176–182)

Key Words: Heart failure, renal dysfunction, chronic kidney disease, beta-blockers, death, hospitalizations, cardiovascular disease, epidemiology.

Current national guidelines recommend that clinicians treat patients with heart failure and left ventricular systolic dysfunction with β -adrenergic receptor blockers (β -blockers),^{1,2} based on robust evidence from several randomized clinical trials showing a reduction in mortality and morbidity. More than two-thirds of patients with heart failure also have chronic kidney disease (CKD),^{3–5} which

independently increases the risk for adverse cardiovascular events and death.^{5–8} Although the majority of earlier clinical trials have either excluded patients with CKD or failed to report baseline kidney function,^{9–13} post hoc analyses of 3 randomized trials of patients with heart failure that included patients with impaired kidney function suggested similar benefit of β -blockers in patients with CKD and without CKD.^{14–16} However, these trials enrolled selected patients and included careful protocol-driven monitoring, so the generalizability of their results to contemporary real-world patients with heart failure and CKD may be limited.

Observational studies using large health care databases that include real-world practice patterns and patient populations can provide complementary evidence to randomized trials. Assessing medication effectiveness outside of a clinical trial setting, however, requires careful methods, because the treatment selection may introduce bias when comparing treatment effects. Approaches such as the “new user” design, which excludes prevalent drug users, reduce the bias introduced by studying chronic users who are more likely

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to be drug tolerant and may have survived longer.¹⁷ Most previous observational studies of β -blockers to treat heart failure in patients with CKD have included prevalent β -blocker users^{4,18,19} and not emphasized a more rigorous new-user design.

To address the limitations of earlier studies regarding β -blockers in patients with CKD and heart failure, we examined whether initiation of β -blockers improves outcomes in a real-world diverse cohort of patients with CKD, newly diagnosed heart failure, and left ventricular systolic dysfunction. We hypothesized that β -blocker use would be independently associated with a lower risk of death and hospitalization due to heart failure.

Methods

Study Cohort

Kaiser Permanente Northern California is a large integrated health care delivery system caring for >3.2 million people who are broadly representative of the local and statewide populations.²⁰ We assembled a cohort of patients with newly diagnosed heart failure and left ventricular systolic dysfunction in the setting of CKD (Fig. 1). We first identified all health plan members aged ≥ 18 years who were diagnosed with newly recognized heart failure, defined as meeting either of the following criteria from January 1, 2006, through December 31, 2008: ≥ 1 inpatient admission with a primary discharge diagnosis of heart failure (*International Classification of Diseases, Ninth Edition* [ICD-9] codes 398.91, 402.01, 402.11, 402.91, 428.0, 428.1, or 428.9); or ≥ 3 outpatient nonemergency department encounters with a diagnosis of heart failure found in billing claims or ambulatory visit databases.

This approach has been previously validated and showed 97% specificity.^{21–23} We excluded patients with <12 months of continuous membership or continuous drug benefit before the index date to ensure more complete information on comorbid conditions and concurrent medication use. We also excluded patients who were missing baseline outpatient serum creatinine, had a history of maintenance dialysis, or had a history of renal or cardiac transplantation.

The index dates were assigned based on the first qualifying criteria for heart failure. For the present analysis, we focused on patients considered to have incident heart failure by excluding any patients with any earlier inpatient or outpatient diagnosis of heart failure up to 10 years before the index date to characterize outcomes from the time of diagnosis and reduce survivor bias. Given the focus on outcomes associated with β -blockers that are indicated for systolic heart failure, we further limited the cohort to patients with left ventricular systolic dysfunction, defined as a qualitative assessment of moderate or severe left ventricular systolic dysfunction, or documented left ventricular ejection fraction $\leq 40\%$, based on cardiac imaging results from echocardiography, radionuclide scintigraphy, cardiac magnetic resonance imaging, or left ventriculography during cardiac catheterization. We classified patients with left ventricular ejection fraction of 30%–40% as having moderate dysfunction and <30% as having severe dysfunction.

Incident β -Blocker Use

With the use of previously validated methods,^{24,25} we characterized longitudinal exposure to the following oral β -blockers: acebutolol, atenolol, betaxolol, bisoprolol, bucindolol, carvedilol, labetalol, metoprolol tartrate, metoprolol succinate, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, and timolol. We based our information from dispensed prescriptions found in health plan ambulatory

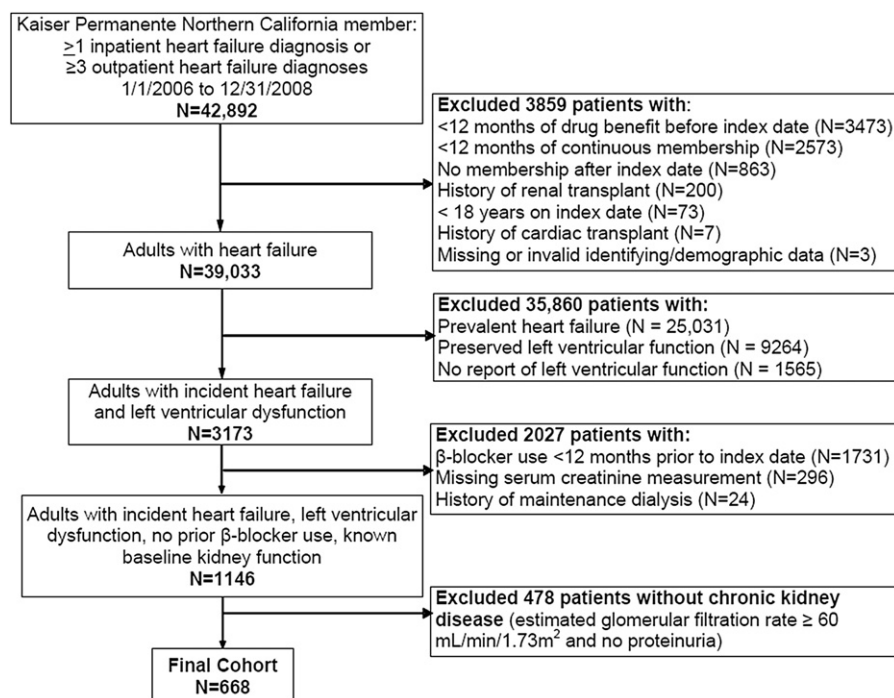


Fig. 1. Cohort assembly of adults with chronic kidney disease, incident heart failure, and left ventricular systolic dysfunction, without previous β -blocker use. The numbers of patients for each exclusion criterion were not mutually exclusive.

pharmacy databases, including estimated day supply information per prescription and the observed refill patterns for β -blockers. Briefly, for any 2 consecutive prescriptions, we examined the time (in days) between the projected end date of the first prescription and the date of the next filled prescription. Because dose adjustment is not uncommon in patients with heart failure, we allowed a “grace period” of 30 days between prescriptions. Thus, if the time between the projected end date of the first prescription and the fill date of the next prescription was ≤ 30 days, we considered that individual to be continually receiving β -blocker therapy. If the refill interval was > 30 days, then the individual was considered to be off β -blocker therapy starting the day after the projected end date of the first prescription until the date of next filled prescription, if any. If > 1 β -blocker prescription was filled on the same day, we used the prescription with the longest estimated day supply. Because the concurrent use of multiple β -blockers is not indicated, patients who filled a prescription for a different β -blocker before the projected end date for an existing β -blocker prescription were considered to have switched to the new β -blocker as of the fill date of the later prescription. We also accounted for the total number of hospital days during follow-up, because hospitalized patients receive medications from the hospital and not their own outpatient supply.

The new-user design minimizes indication and underascertainment biases that can occur in observational studies of comparative effectiveness.^{17,26} We therefore excluded patients with any evidence of β -blocker use within 12 months before the index date. We chose a 12-month window to ensure a uniform ascertainment period, because all patients had ≥ 12 months of continuous drug benefit to be included in the study cohort. As a sensitivity analysis, we repeated the analyses with a longer ascertainment window, excluding patients with any evidence of β -blocker use within 5 years before the index date.

Assessment of Kidney Function

Baseline serum creatinine was measured with an isotope dilution mass spectrometry—traceable assay²⁷ within 1 year before or on the index date. We calculated the estimated glomerular filtration rate (GFR) with the use of the Chronic Kidney Disease Epidemiology Collaboration equation.²⁸ Proteinuria was defined as an albumin-to-creatinine ratio > 30 mg/g or urinary dipstick protein excretion $\geq 1+$, in the absence of concomitant nitrate or leukocyte esterase positivity (to exclude patients with a possible urinary tract infection). We coded proteinuria as absent when proteinuria information was missing. We defined CKD as either the presence of proteinuria or estimated GFR < 60 mL min⁻¹ 1.73 m⁻², or both.

Follow-Up and Ascertainment of Clinical Outcomes

Patients were followed until the time of health plan disenrollment, initiation of dialysis, or August 31, 2010. The primary outcome was death from any cause, identified from health plan databases (inpatient deaths, proxy report of outpatient deaths), annual California state death certificate files, and quarterly updated Social Security Administration Vital Status Files.^{29,30} The secondary outcome of interest was a combined end point of time to death or first hospitalization for heart failure, using the ICD-9 codes as listed above.

Covariates

Data on age, sex, and self-reported race or ethnicity were obtained from health plan databases. We ascertained data on

comorbid conditions up to 4 years before the index date and throughout the duration of follow-up, using previously validated approaches based on ICD-9 diagnosis and procedure codes and Current Procedure Terminology codes.^{21,22,31–35} The following comorbid conditions were identified: coronary heart disease (acute myocardial infarction, unstable angina, percutaneous coronary intervention, or coronary artery bypass surgery), other cardiovascular disease (hospitalized ischemic stroke, transient ischemic attack, cerebrovascular disease, peripheral arterial disease, or valvular heart disease), atrial fibrillation or flutter, diabetes mellitus, hypertension, dementia or depression, thyroid disease, systemic cancer, and chronic lung disease. We ascertained ambulatory measurements of body mass index, systolic blood pressure, estimated GFR, and serum hemoglobin up to 1 year before or on the index date and for the duration of follow-up.

We characterized baseline and longitudinal exposure to other relevant cardiovascular medications with the use of similar methods as described above for β -blockers, based on information from pharmacy records for the following: angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium channel blockers, diuretics, lipid lowering agents, and antiplatelet agents (including aspirin).^{22,23}

Statistical Analysis

All analyses were performed with the use of SAS statistical software, version 9.2 (Cary, North Carolina). We examined the univariate associations of the covariates listed above with β -blocker initiation after study entry in Cox regression models. Our primary analysis examined β -blocker use versus nonuse in a time-varying (ie, “as-treated”) manner. That is, patients can initiate or discontinue the β -blocker during the follow-up time. As shown in Figure 2, no patients are on β -blockers at cohort entry, owing to our new-user design. On day 1, both patient 1 and patient 2 initiate β -blockers. Whereas patient 1 remains on the β -blocker until his death on day 150, patient 2 stops the β -blocker on day 31 and restarts it on day 91, staying on it until his death at day 150. Both patients have a heart failure hospitalization on day 85. In the time-varying model, patient 1 is categorized as a user at the time of heart failure hospitalization, whereas patient 2 is categorized as a nonuser at the time of heart failure hospitalization and a user at the time of death. We also conducted a companion analysis wherein β -blocker use was analyzed with the use of an “intention-to-treat” approach. In this case, once patients initiate a β -blocker, they remain categorized as a user, regardless of whether they subsequently discontinue the medication during observed follow-up. In the intention-to-treat model in Figure 2, both patients are categorized as users at the time of heart failure hospitalization and at the time of death.

We used extended Cox regression models with a robust sandwich covariance estimator to evaluate the independent association between incident β -blocker use and outcomes. We first looked at unadjusted associations and then conducted a series of nested models which adjusted for baseline, time-updated, and time-varying variables. For example, if a patient developed diabetes during the follow-up period, his set of comorbid conditions would be “updated” to reflect the fact that he now had diabetes mellitus. Once a patient developed a comorbid condition, he could not go back to not having that condition. In contrast, values for time-varying variables, such as body mass index, blood pressure, or other relevant medication use were allowed to change values during follow-up. In model 1, we adjusted for

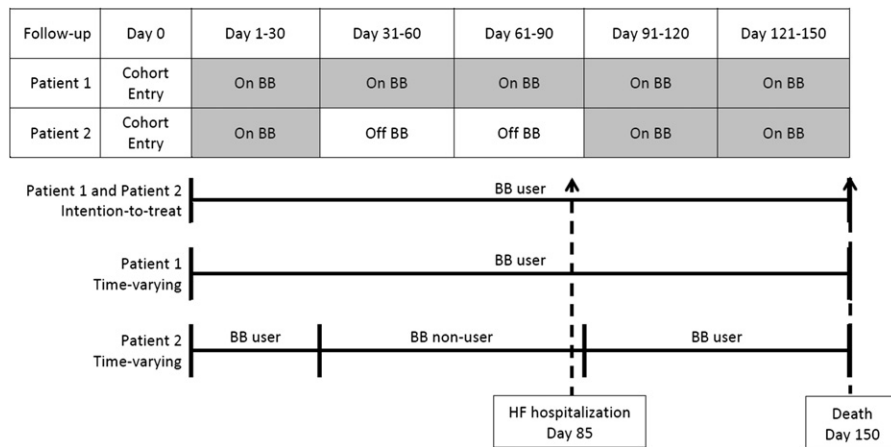


Fig. 2. Conceptual models of intention-to-treat and time-varying models of β -blocker therapy. In this example, in the intention-to-treat models, both patient 1 and patient 2 are categorized as “users” at the time of heart failure hospitalization on day 85 and at the time of death on day 150. In the time-varying model, patient 2 is categorized as a “nonuser” at the time of heart failure hospitalization and a “user” at the time of death. BB, β -blocker; HF, heart failure.

race (white/European, black/African American, other), sex, and baseline smoking status (yes vs no), left ventricular systolic dysfunction (moderate vs severe), proteinuria (yes vs no), time-updated age and comorbid conditions (present vs absent), time-varying body mass index category, systolic blood pressure, estimated GFR category, and hemoglobin (per 1 g/dL). These variables were selected because they were previously reported to be associated with death or heart failure hospitalization, or they differed between CKD and non-CKD groups at baseline with the use of a $P < .05$ cutoff. In model 2, we additionally adjusted for time-varying use of other relevant cardiovascular medications.

The Institutional Review Boards of the Kaiser Foundation Research Institute and Stanford University approved the study. A waiver of informed consent was obtained due to the nature of the study.

Results

We identified 668 eligible patients during the study period with incident heart failure, left ventricular systolic dysfunction and no evidence of previous β -blocker use (Fig. 1). At cohort entry, a majority of patients had CKD stage 3a or 3b (estimated GFR 30–59 mL min⁻¹ 1.73 m⁻²; Table 1). During a median of 2.4 years (interquartile range [IQR] 1.0–3.4 years) of follow-up, 74% of patients initiated β -blocker therapy, most commonly carvedilol (42%), metoprolol tartrate (21%), and atenolol (4%). The median time to β -blocker initiation was 10 days (IQR 4–47 days) after the incident heart failure diagnosis. The likelihood of β -blocker initiation declined with increasing category of age, such that patients ≥ 80 years old were 41% less likely to start a β -blocker compared with patients < 50 years old (Table 1). Patients with the highest baseline systolic blood pressure (≥ 160 mm Hg) were more likely to initiate β -blockers than patients with systolic blood pressure < 120 mm Hg.

Initiation of β -Blocker Therapy and Death

There were a total of 195 deaths during follow-up: 126 deaths in patients who initiated a β -blocker and 69 deaths in the nonuser group. Incident β -blocker use was associated with a significantly lower risk of death for patients in unadjusted models (Fig. 3, unadjusted model). Adjusting for differences in patient characteristics, laboratory values, and comorbid conditions did not materially change our results (Fig. 3, model 1). Adjustment for time-varying exposure to other relevant cardiovascular medications attenuated the association of β -blocker use with death, which no longer was statistically significant (Fig. 3, model 2). Our results were qualitatively similar in sensitivity analyses that examined β -blocker use as an intention-to-treat variable (fully adjusted hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.50–0.98) and that excluded patients with any β -blocker use up to 5 years before the index date (data not shown).

Initiation of β -Blocker Therapy and Death or Heart Failure Hospitalization

There were a total of 470 heart failure hospitalizations during follow-up: 411 in β -blocker users and 59 in nonusers. In unadjusted analyses, incident β -blocker use was associated with a lower risk of death or heart failure hospitalization in unadjusted and adjusted models (Fig. 3). Our results were not materially changed in sensitivity analyses that examined β -blocker use as an intention-to-treat variable (fully adjusted HR 0.82, CI 0.63–1.05) and that excluded patients with any β -blocker use up to 5 years before the index date (data not shown).

Discussion

Initiation of β -blocker therapy was associated with a lower risk of death or heart failure hospitalization in this contemporary diverse cohort of patients with CKD,

Table 1. Baseline Characteristics of 668 Adults With Chronic Kidney Disease, Incident Heart Failure, and Left Ventricular Systolic Dysfunction, and Their Univariate Associations With β -Blocker Initiation

	Total Cohort (n = 668)	Univariate HR (95% CI)
Estimated GFR ($\text{mL min}^{-1} 1.73 \text{ m}^{-2}$)		
90–150 (CKD stage 1)	3.4	(ref)
60–89 (CKD stage 2)	11.2	1.07 (0.63–1.80)
45–59 (CKD stage 3a)	49.7	0.95 (0.60–1.51)
30–44 (CKD stage 3b)	28.7	0.97 (0.60–1.57)
<29 (CKD stages 4 & 5)	6.3	1.07 (0.61–1.90)
Age (y)		
<50	6.1	(ref)
50–59	12.1	0.80 (0.52–1.24)
60–69	16.3	0.81 (0.53–1.22)
70–79	27.0	0.64 (0.43–0.93)
≥ 80	38.5	0.59 (0.40–0.87)
Female, %	33.5	1.02 (0.85–1.23)
Race, %		
White/European	71.3	(ref)
Black/African American	11.4	1.03 (0.80–1.32)
Other	17.4	0.88 (0.69–1.13)
Current or former smoker, %	33.7	1.08 (0.90–1.30)
Comorbid conditions, %		
Coronary heart disease	4.2	0.91 (0.62–1.33)
Other cardiovascular disease	24.6	0.89 (0.72–1.11)
Atrial fibrillation or flutter	22.8	1.10 (0.88–1.37)
Diabetes mellitus	37.0	0.90 (0.75–1.08)
Hypertension	63.9	0.93 (0.77–1.11)
Dementia or depression	18.3	1.06 (0.84–1.33)
Thyroid disease	12.7	1.07 (0.83–1.39)
Cancer	16.0	1.08 (0.84–1.39)
Chronic lung disease	30.2	0.95 (0.79–1.15)
Vital Signs, %		
Body mass index (kg/m^2)		
<24.9	27.1	(ref)
25–29.9	29.0	1.17 (0.92–1.49)
≥ 30	30.5	1.11 (0.88–1.41)
Unknown	13.3	1.34 (0.97–1.85)
Systolic blood pressure (mm Hg)		
<120	33.8	(ref)
120–129	16.3	0.89 (0.68–1.17)
130–139	21.1	1.13 (0.89–1.45)
140–159	13.9	0.88 (0.66–1.16)
>160	9.3	1.42 (1.05–1.93)
Unknown	5.5	1.63 (0.96–2.75)
Baseline medication use, %		
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	41.3	1.02 (0.85–1.21)
Diuretics	52.4	0.81 (0.68–0.97)
Lipid-lowering agents	39.8	0.89 (0.74–1.06)
Antiplatelet agents	4.8	0.71 (0.43–1.16)
Calcium channel blockers	52.4	0.98 (0.79–1.21)
Hemoglobin (g/dL)		
<9.0	2.7	1.66 (0.82–3.35)
9.0–9.9	2.8	0.82 (0.41–1.61)
10.0–10.9	5.8	1.07 (0.68–1.68)
11.0–11.9	11.5	(ref)
12.0–12.9	15.6	0.89 (0.62–1.27)
13.0–13.9	17.1	1.04 (0.74–1.47)
≥ 14.0	35.6	1.17 (0.86–1.61)
Severe left ventricular systolic dysfunction, %	49.7	1.20 (1.01–1.44)

newly diagnosed heart failure, and left ventricular systolic dysfunction. These associations were attenuated for the outcome of death alone after extensive statistical adjustment for potential confounders, but they remained statistically

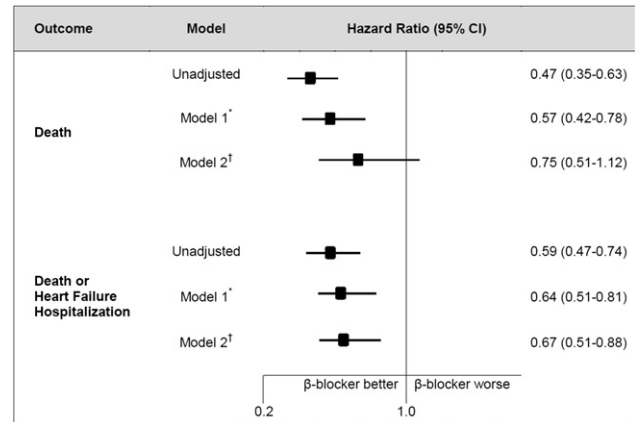


Fig. 3. Association of time-varying β -blocker therapy with death and heart failure hospitalization in adults with chronic kidney disease, incident heart failure, and left ventricular systolic dysfunction. *Model 1: adjusted for baseline race, sex, smoking status, left ventricular systolic function, proteinuria, time-updated age, comorbid conditions, time-varying body mass index category, systolic blood pressure, estimated glomerular filtration rate category, and hemoglobin. †Model 2: model 1 plus time-varying use of other relevant cardiovascular medications. CI, confidence interval.

significant for the combined end point of death or heart failure hospitalization.

Our findings are consistent with secondary analyses of several randomized clinical trials. For example, a recent post hoc analysis of pooled individual patient data from the CAPRICORN (Carvedilol Postinfarct Survival Control in Left Ventricular Dysfunction Study) and COPENICUS (Carvedilol Prospective Randomized Cumulative Survival) studies showed treatment with carvedilol versus placebo was associated with a 61% (CI 19%–57%) lower risk of death in patients without CKD (defined as estimated GFR $\geq 60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$) and a 24% (CI 7%–37%) lower risk of death in patients with CKD.³⁶ Similarly, in CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) the 34% (CI 19%–56%) lower risk of death in the β -blocker-treated group compared with placebo was consistent across a limited range of renal function.¹⁵ In our analysis, β -blocker initiation was associated with lower risks of death in patients with CKD, suggesting that the findings from the tightly controlled setting of a clinical trial can be extended to the real-world clinical practice setting.

An important feature of the present study is its use of a new-user design, which is the preferred method to minimize different biases when examining medication effectiveness in observational data.¹⁷ Earlier observational studies did not restrict patients to new users of β -blockers to treat heart failure in CKD.^{3,19} Our study followed patients from the initial documented diagnosis of heart failure and time of β -blocker initiation, which provided a comprehensive assessment of the patient's clinical experience and minimized selection bias and underascertainment biases. We also examined a population that is more broadly representative of community care patterns than the referral cardiology clinics

captured by previous studies.^{3,19} Taken together, our study strengthens the validity and broadens the applicability of earlier results and suggests a beneficial association of β-blockers with clinical outcomes among a wide range of patients with CKD, heart failure, and left ventricular systolic dysfunction in a contemporary treatment era.

This study also has several limitations. First, as an observational study of outcomes associated with different treatment strategies, we can not completely rule out residual confounding. For example, we did not have information on functional status, heart rate or rhythm, general frailty, provider characteristics, patient refusal of additional therapies, and other clinical characteristics, such as severity of chronic lung disease, that may have influenced β-blocker initiation and outcomes. We did, however, have comprehensive longitudinal data on follow-up use of other relevant cardiovascular medications, relevant laboratory values, and comorbid conditions, allowing us to account for these important potential confounders in a time-varying fashion. Second, our results may be of limited generalizability to the overall population of patients who develop incident heart failure. By excluding prevalent β-blocker users, the remaining cohort had a relatively low prevalence of coronary heart disease. Also, although recommended by current guidelines,² fewer than one-half of patients in our cohort were using renin-angiotensin system inhibitors at baseline, and during follow-up very few (8.8%) initiated either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker. Third, by focusing on a contemporary cohort with follow-up through 2010, the trade-off was a median follow-up time of just 2.4 years, and we do not have longer-term follow-up data. Finally, although more than one-third of our study population had an estimated GFR $<45 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, relatively few patients had stage 4–5 CKD, which limited our ability to examine the relative effectiveness of β-blockers in patients in the most advanced stages of non-dialysis-dependent CKD.

In conclusion, our analysis supports the use of β-blockers in patients with heart failure and left ventricular systolic dysfunction complicated by CKD. Because patients with heart failure and CKD have a high absolute risk of adverse events, they could potentially experience even greater absolute benefits from β-blocker treatment than patients with normal kidney function. Future randomized trials of β-blocker therapy for heart failure, particularly in patients with the most advanced stages of CKD, are needed to inform the treatment of this very high-risk population.

Disclosures

None.

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