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Indications for Beta-blocker Prescriptions in Heart Failure With Preserved Ejection Fraction

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Abstract

Objectives: To better understand indications for beta-blocker prescriptions among older adults hospitalized with heart failure with preserved ejection fraction (HFpEF)

Design/Setting: Retrospective observational study of hospitalizations derived from the geographically-diverse REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort.

Participants: We examined Medicare beneficiaries aged ≥ 65 years with an expert-adjudicated hospitalization for HFpEF (left ventricular ejection fraction ≥ 50%).

Measurements: Discharge medications and indications for beta-blockers were abstracted from medical records.

Results: Of 306 hospitalizations for HFpEF, beta-blockers were prescribed at discharge in 68%. Among hospitalizations resulting in beta-blocker prescriptions, 60% had a compelling indication for beta-blocker—44% had arrhythmias and 29% had myocardial infarction history. Among the

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All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Dr. Yum and Dr. Goyal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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The other authors report no conflicts.

40% with neither indication, 57% had CAD without MI and 38% had hypertension alone (without arrhythmia, MI, or CAD), both clinical scenarios with little supportive evidence of benefit of beta-blockers. Among hospitalizations resulting in beta-blocker prescription at discharge, 69% had geriatric conditions (functional limitation, cognitive impairment, hypoalbuminemia, or history of falls). There were no significant differences in the prevalence of geriatric conditions between hospitalizations of individuals with compelling indications for beta-blockers and hospitalizations of individuals with non-compelling indications.

Conclusions: Beta-blockers are commonly prescribed following a hospitalization for HFpEF, even in the absence of compelling indications. This occurs even for hospitalizations of individuals with geriatric conditions, a subpopulation that may be at elevated risk for experiencing harm from beta-blockers.

Keywords

Diastolic heart failure; beta-blocker; adverse reactions

Introduction

Heart failure with preserved ejection fraction (HFpEF) affects over 3 million adults in the United States (US), accounting for 50% of all of heart failure (HF).¹ While several medications including beta-blockers (BBs) and renin-angiotensin inhibitors have yielded improved outcomes in HF with reduced ejection fraction (HFrEF) and are key pillars of its management,² no medications have consistently improved outcomes in HFpEF.³ Despite lack of data supporting their benefits, medications commonly used for HFrEF such as BBs are frequently prescribed for HFpEF.^{4,5} Indeed, in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study, almost 80% of participants with HFpEF took BBs.⁴

There is cause for concern regarding the use of BBs in adults with HFpEF. Not only have they failed to improve clinical endpoints in randomized controlled trials (RCTs),^{6–8} but BBs may actually cause harm in HFpEF through a number of potential mechanisms. First, they can exacerbate chronotropic incompetence, which is defined as the inability to increase one's heart rate commensurate with physiologic need, and is a common physiologic mechanism underlying HFpEF.^{9,10} Second, BBs are a common cause of adverse drug reactions.¹¹ Third, BBs can worsen function in the setting of geriatric conditions,¹² an important consideration for HFpEF which is a condition that disproportionately affects older adults.¹³ Given the high prevalence of BB use in HFpEF despite the paucity of data to support its benefit and the presence of several potential mechanisms for causing harm, we sought to examine hospitalizations for HFpEF in an unselected national cohort of older adults to better understand indications for BB prescriptions in HFpEF. We hypothesized that BB prescriptions would be common even in the absence of compelling indications.

Methods:

We conducted this study in the context of the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a geographically-diverse prospective

observational cohort of 30,239 community-dwelling white and black men and women from across the United States with oversampling of the South, originally recruited in 2003–2007 with ongoing follow-up.¹⁴ We studied a sample of HFpEF hospitalizations between 2003 and 2014. We defined hospitalizations for HFpEF as HF-hospitalizations (adjudicated by expert clinical adjudicators), with documented left ventricular ejection fraction (LVEF)

50%,² obtained from diagnostic studies such as echocardiograms and progress notes through chart review. In cases where the LVEF was not documented during the hospitalization, we used LVEF from prior hospitalizations within 6 months. Given that the focus of performance metrics and quality improvement efforts such as medication optimization have been at the level of the hospital, we examined unique hospitalizations rather than unique patients in this study. We included only repeat hospitalizations that occurred beyond 90 days of an eligible hospitalization since repeat hospitalizations in close proximity of another hospitalization are likely to occur at the same hospital¹⁵ (with care from the same clinicians). We excluded hospitalizations for individuals with a history of LVEF<40% (n=10), for whom neurohormonal antagonists including BBs are beneficial.¹⁶

This study included data from 3 sources—REGARDS baseline assessment, REGARDS-MI ancillary study adjudication database, and hospitalization-based medical records. Socio-demographics and geriatric conditions (functional limitation, cognitive impairment, hypoalbuminemia, and history of falls,) came from the REGARDS baseline assessment. We defined functional limitation as a ShortForm-12 physical component summary score<30; cognitive impairment as a six-item screener score<5;¹⁷ hypoalbuminemia (a marker for frailty) as serum albumin <3.3g/dL¹⁸; and history of falls as having 1 self-reported fall in the prior year. We abstracted data from medical records using a structured tool and a quality-controlled protocol, collecting data on comorbid conditions, hospital events, and clinical parameters and medications at hospital discharge.

We classified indications for BBs into 2 groups based on clinical practice guidelines and the evidence supporting these indications—“compelling” indications, for which BBs have Class I indications, included atrial^{19,20} and ventricular arrhythmias;²¹ history of myocardial infarction (MI);²² and “non-compelling” indications included coronary artery disease (CAD) in the absence of an MI, hypertension, and “unknown” for which there was no clear indication.

For all analyses, we used generalized estimating equations. We specified an independent correlation structure and utilized linear regression for continuous variables and logistic regression for categorical variables, using a Huber sandwich estimator of the standard errors to account for clustering related to repeat hospitalizations experienced by the same participant. We calculated medians with interquartile ranges (IQR) for continuous variables and percentages for categorical variables. We considered $p<0.05$ as statistically significant. We performed analyses using R-version 3.5.1 (<http://www.R-project.org>).

Results:

We examined 306 hospitalizations for HFpEF from 202 unique hospitals across the US among 254 unique participants (85% experienced 1 hospitalization; 15% experienced 2–5

hospitalizations with a median of 2. We observed a median of 1 (IQR 1–1) unique participant and 1 (IQR 1–2) hospitalization per hospital. A third (13/39) of unique participants with multiple hospitalizations were prescribed BB at discharge for one hospitalization but not a subsequent or prior hospitalization, supporting our approach to examine unique hospitalizations in this analysis.

We found 68% of hospitalizations resulted in BB prescriptions at hospital discharge (Table 1). Among these, 87% were taking BB at hospital admission. The most common BB prescribed was metoprolol (47%), followed by carvedilol (32%). Among hospitalizations resulting in BB prescription at discharge, 60% had compelling indications for BBs—44% had arrhythmias (43% atrial arrhythmia, 4% ventricular arrhythmia) and 29% had MI history (Figure 1). On the other hand, 40% of HFpEF hospitalizations had neither of these indications. Among those with neither indication, 57% had CAD in the absence of MI and 38% had hypertension alone (without arrhythmia, MI, or CAD)—two non-compelling indications for BB. Approximately 5% had no documented indication. Among hospitalizations of patients with CAD without MI who were taking BB, 77% were taking aspirin and 79% were taking a statin, two agents with Class I indications for CAD regardless of MI status.²² Among those with hypertension alone, 52% were on a BB with alpha-blocking activity (carvedilol and labetalol), a subclass that may be especially effective at treating hypertension; and 71% were on an angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB), which may be superior to BBs for both hypertension²³ and HFpEF.^{24,25}

Among hospitalizations resulting in the prescription of BBs at discharge, 69% had geriatric conditions: 26% had functional limitation, 14% had cognitive impairment, 38% had hypoalbuminemia, and 26% had a history of falls. There were no significant differences in the prevalence of geriatric conditions between hospitalizations of individuals with versus without compelling indications for BBs (Figure 2).

Discussion:

Our study shows that BB prescription at discharge for a HFpEF hospitalization is common among older adults, despite a paucity of data to support BB use in HFpEF. To date, RCTs of BBs have failed to demonstrate improvements in mortality, hospitalization rates, quality of life, or echocardiographic parameters.^{6–8} Yet, two of three HFpEF hospitalizations from this geographically diverse real-world cohort (spanning >200 hospitals) resulted in the prescription of BBs at hospital discharge. This finding is consistent with data from large RCTs^{4,5} which have shown a prevalence of BB use as high as 80%. These observations could relate, at least in part, to misconceptions about the pathophysiology of HFpEF.²⁶ Whereas some have suggested that slowing down the heart rate can improve filling and ameliorate the negative effects of diastolic dysfunction, there is a contrasting notion that BBs can worsen chronotropic incompetence, which plays an important role in the pathophysiology of HFpEF, and can potentially worsen cardiac output.^{9,10} In addition, slowing heart rate in a predominantly older population can exacerbate age-related changes to the conduction system, and subsequently increase susceptibility to bradyarrhythmias.^{27,28} Accordingly, BBs may actually be harmful in HFpEF.

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An alternative reason for the common use of BBs in HFpEF could be that individuals with HFpEF have other conditions that warrant BB use such as arrhythmia^{19–21} and/or MI history.²² Our study found that this only partly explained the high prevalence of BB prescription at hospital discharge; over one third of HFpEF hospitalizations with BB prescription at discharge did not have a compelling indication like arrhythmia or MI. Although an additional proportion of these hospitalizations included patients with CAD without MI, and/or hypertension, the data supporting the use of BBs for these conditions are limited. With regard to CAD, an observational study of 44,000 patients using propensity-matching revealed that BBs did not reduce cardiovascular events among those with CAD without a history of MI.²⁹ With regard to hypertension, a recent Cochrane review of RCTs revealed BBs to have little to no effect on mortality and an overall effect that was inferior to other antihypertensive drugs.²³ Interestingly, we found that almost a quarter of the hospitalizations with BB prescription for CAD (no history of arrhythmia or MI) did not result in aspirin prescription and a quarter did not result in statin prescription at discharge, two agents with Class I indications for CAD regardless of MI status.²² We also found that almost a quarter of hospitalizations with BB prescriptions for hypertension did not result in the prescription of ACEIs or ARBs at discharge; ACEIs and ARBs may be superior in preventing stroke for those with hypertension,²³ and may be superior in preventing hospitalizations in HFpEF.^{24,25} Although these findings could relate to contraindications or patient preferences, they could also reflect suboptimal prescribing practices that warrant attention.

In our study, we also found that over two-thirds of hospitalizations resulting in a BB prescription at discharge involved patients with geriatric conditions. This is important because BBs may worsen functional parameters among older adults with geriatric conditions.¹² In a study of over 15,000 nursing home residents, BBs were associated with functional decline specifically among those with cognitive or functional impairment. Furthermore, BBs increase the risk for adverse drug reactions requiring a hospitalization,^{11,30} and thus may not be ideal for individuals with geriatric conditions who are at high risk for experiencing adverse drug reactions.³¹ Accordingly, the risk-benefit ratio of BBs, especially for individuals who lack compelling indications, may favor harm in many HFpEF patients. Unfortunately, we found that the rates of geriatric conditions were similar regardless of having a compelling indication. Strategies are needed to facilitate patient-physician communication and shared decision-making with regard to BBs in HFpEF, especially given the uncertainty of their risks and benefits.

An important consideration regarding the common prescription of BBs in HFpEF is the paucity of evidence to guide BB discontinuation. This is particularly relevant since we found that the majority of BBs prescribed at discharge were a continuation of BBs taken at hospital admission. Studies from two decades ago showed that BB withdrawal can cause MI or even death,³² which led to a black-box US Food and Drug Administration warning. Given the potential for harm, clinicians may not know how to safely discontinue BBs. This underscores the need to develop protocols for the safe discontinuation of BBs when the risks outweigh the potential benefits, a priority recently enumerated by an expert panel of physicians and pharmacists.³³

Strengths of this study include the geographically-diverse nationwide sample of unselected hospitalizations from 202 different hospitals across the US. Another strength was the depth of medical record review that included abstraction of over 60 comorbid conditions, allowing determination of potential indications for BB prescription. We were also able to detect geriatric syndromes, which are important risk indicators. Some limitations should also be considered. The sample size for this study was relatively small, which limited statistical power to detect small to moderate differences between groups. Since medical record review relies on documentation of comorbid conditions and medications, misclassification of BB indications was possible. Also, we could not be sure that inferences regarding indications for BB prescriptions reflected the thinking of the prescribing clinicians. We could not reliably detect angina, which could be a reasonable indication for BB even in the absence of MI history. We also did not have data on the timing of prior MI—given data to suggest that BBs are beneficial for approximately 3 years following an MI,²² our data on the prescription of BBs for a history of MI as a compelling indication may be an overestimation.

Conclusion:

BBs are commonly prescribed following HFpEF hospitalizations among older adults in the absence of compelling indications. This occurs even when geriatric conditions are present, which is concerning because BBs can worsen function in patients with geriatric conditions and can increase their risk for adverse drug reactions. Future study is needed to identify the underlying reasons for these prescribing patterns and develop strategies to reduce the use of BB in subpopulations that may experience harm.

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Figure 1: Indications for BBs prescribed at discharge following a HFpEF hospitalization.

A significant proportion (40%) of HFpEF hospitalizations resulting in BB prescriptions at hospital discharge did not have a compelling indication (arrhythmia or history of MI) for BB. Among those with a non-compelling indication, 57% had CAD in the absence of MI and 38% had hypertension alone (without arrhythmia, MI, or CAD). Abbreviations: BB- Beta blocker; HFpEF-heart failure with preserved ejection fraction; CAD-coronary artery disease; MI-myocardial infarction

Figure 2: Prevalence of geriatric conditions according to indications for BB

Among HFpEF hospitalizations resulting in the prescription of BBs at discharge, the prevalence of geriatric conditions including functional limitation, cognitive impairment, hypoalbuminemia, and a history of falls are shown according to the presence of compelling (arrhythmia or history of MI) or non-compelling (CAD in the absence of MI, hypertension, or unknown) indications. There were no significant differences in the prevalence of geriatric conditions between those with compelling indications for BBs and those with non-compelling indications. Abbreviations: BB-Beta blocker; HFpEF-heart failure with preserved ejection fraction; CAD-coronary artery disease; MI-myocardial infarction

Table 1.

Study Population According to Beta-blocker Use at Hospital Discharge

Variable	All (n=306)	Discharged on BB (n=207)	Not Discharged on BB (n=99)	P-value
Age, median (IQR)	76 (72–83)	77 (72–84)	76 (71–81)	0.17
Female, n (%)	170 (56)	113 (55)	57 (58)	0.65
White, n (%)	187 (61)	124 (60)	63 (64)	0.57
Income less than \$20K	111 (42)	78 (43)	33 (39)	0.55
Education less than high school	83 (27)	61 (30)	22 (22)	0.25
Comorbid conditions, n (%)				
Charlson Comorbidity Index, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.05
Hypertension	254 (83)	182 (88)	72 (73)	0.002
Coronary artery disease	195 (64)	144 (70)	51 (52)	0.004
Diabetes Mellitus	154 (50)	105 (51)	49 (50)	0.85
Atrial fibrillation/flutter	133 (44)	89 (43)	44 (44)	0.82
Chronic obstructive pulmonary disease	130 (43)	77 (37)	53 (54)	0.01
Chronic Kidney Disease	127 (42)	95 (46)	32 (32)	0.04
Anemia	109 (36)	75 (36)	34 (34)	0.75
Cancer	56 (18)	41 (20)	15 (15)	0.36
History of myocardial infarction	56 (18)	45 (22)	11 (11)	0.04
Stroke	55 (18)	46 (22)	9 (9)	0.006
Peripheral vascular disease	53 (17)	34 (16)	19 (19)	0.56
Depression	37 (13)	25 (12)	12 (12)	0.99
Ventricular tachycardia/fibrillation	16 (5)	9 (4)	7 (7)	0.33
Geriatric Assessment, n (%)				
Functional limitation	84 (30)	54 (29)	30 (33)	0.48
Cognitive impairment	42 (15)	30 (15)	12 (14)	0.85
Hypoalbuminemia	119 (54)	78 (50)	41 (61)	0.14
History of Falls	77 (25)	53 (26)	24 (24)	0.80
Hospital Events				
Length of Stay, median (IQR)	5 (3–8)	5 (3–7)	5 (3–8)	0.16
Intensive Care Unit Stay, n (%)	58 (19)	42 (20)	16 (16)	0.40
Cardiology Consult, n (%)	202 (66)	132 (64)	70 (71)	0.24
Discharge to Home, n (%)	180 (78)	122 (78)	58 (80)	0.79
Discharge Parameters, median (IQR)				
Systolic Blood Pressure, mmHg	128 (112–148)	131 (114–150)	122 (110–144)	0.07
Heart Rate, beats per minute	72 (65–84)	70 (63–82)	75 (67–85)	0.10
Total Medication Count	10 (8–13)	11 (9–14)	9 (7–11)	<0.001
ACEI/ARB use, n (%)	165 (54)	122 (59)	43 (43)	0.01
Aspirin use, n (%)	180 (59)	124 (60)	56 (57)	0.59

Variable	All (n=306)	Discharged on BB (n=207)	Not Discharged on BB (n=99)	P-value
Statin use, n (%)	164 (54)	127 (61)	37 (37)	<0.001
Hospital characteristics				
Urban	203 (76)	136 (76)	67 (77)	0.81
Teaching Hospital	135 (44)	88 (43)	47 (48)	0.45

Abbreviations: Beta-blocker (BB); Interquartile range (IQR); Angiotensin converting enzyme inhibitor (ACEI); Angiotensin receptor blocker (ARB)