Frequency of Utilization of Beta Blockers in Patients With Heart Failure and Depression and Their Effect on Mortality

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Beta blockers reduce mortality and morbidity in patients with heart failure. Early reports linking β-blockers with depression may have limited their use in heart failure patients with co-morbid depression. Although more recent studies have challenged the association between β-blocker therapy and depression, patient and physicians remain concerned. The goal of this study is to evaluate the utilization and outcomes of β-blocker therapy in heart failure patients with depression. This is a retrospective cohort study of patients at a multicenter integrated healthcare system with a diagnosis of heart failure from 2008 to 2014. Among 6,915 patients with heart failure with left ventricular ejection fraction of <50%, 1,252 (18.1%) had a diagnosis of depression. Patients with depression were more likely to be women and had a higher prevalence of cardiovascular risk factors. Depression was associated with decreased odds of β-blocker treatment (adjusted odds ratio [OR], 0.77; 95% confidence interval [CI], 0.62 to 0.95; p = 0.016). During a mean follow-up of 2.6 years, 439 (35.1%) patients with depression died compared with 1,549 (27.4%) patients without depression. Depressed patients not treated with β-blocker had higher mortality compared with nondepressed patients (adjusted hazard ratio [HR], 1.4, 95% CI 1.09 to 1.7, p = 0.005). When treated with β-blockers, their risk of mortality was attenuated (HR 1.1, 95% CI 0.97 to 1.2, p = 0.14). In conclusion, β-blocker therapy remains underutilized in heart failure patients with depression, and its underutilization contributes to the reduced survival rate observed in this cohort. **(Am J Cardiol 2019;124:746−750)**

Heart failure in the United States is a major public health issue with a prevalence of over 5.8 million people. The lifetime risk of heart failure is around 1 in 5, although improvements in understanding of the underlying disease as well as treatments have raised the expected lifespan.[1,2] Beta blockers are the cornerstone treatment for chronic heart failure. Randomized trials showed that β-blockers reduce mortality and morbidity in patients with heart failure and they are recommended by the American College of Cardiology/American Heart Association guidelines.[1] Early reports from the 1960s and 1980s raised concerns that β-blockers may cause depression.[3,4] Recent studies that utilized more rigorous methodologies have challenged this idea, and showed no association between β-blocker therapy and depression, suggesting that restricting β-blocker use in patients with depression may be unwarranted.[5,6] Nevertheless, continued patient and physician concerns may contribute to their underutilization in heart failure patients with depression. This is an important issue because over 20% of heart failure patients in the United States suffer from depression and this group of patients has significantly worse clinical outcomes.[7,8] The goal of this study is to evaluate the utilization of β-blocker therapy in heart failure patients with co-morbid depression, and to evaluate the effect of β-blocker therapy on mortality in heart failure patients with or without depression.

Methods

This is a retrospective cohort study based on data from the Kaiser Permanente Southern California (KPSC) health system, an integrated healthcare system serving more than 4 million members. Members enroll through the Kaiser Foundation Health Plan for comprehensive medical insurance that includes pharmacy benefits.

Comprehensive information on the medical care KPSC members receive is prospectively captured electronically through a centralized data warehouse, with electronic data sets with linked information on demographics, administrative, pharmacy, laboratory, and health care utilization data from both ambulatory visits and hospitalizations. The present study was approved by the KPSC Institutional Review Board. A waiver of informed consent was obtained because of the observational nature of the study.

Patients aged ≥21 years diagnosed with heart failure from January 1, 2008 to December 31, 2014 were identified using International Classification of Diseases (ICD-9-CM) codes 428.x, 402.x, and 404.x3. Patients were included in the study if they had at least one inpatient diagnostic code for heart failure, or at least 2 outpatient encounters with a diagnosis of heart failure. The date of first diagnosis of heart failure was used as the index date. Patients who were

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not members or with less than 1 year of health plan enrollment prior to the index date were excluded. Patients with less than 7 days of follow-up time were excluded to allow adequate follow-up. Patients with no echocardiogram information were excluded.

Left ventricular ejection fraction (LVEF) assessments were based on transthoracic echocardiography. LVEF was extracted from the first transthoracic echocardiogram report obtained after the index date. Patients were classified as having heart failure with systolic dysfunction if their LVEF was <50%. Patients with LVEF ≥50% were excluded due to lack of evidence to support β-blocker therapy in this group.

Co-morbidities at baseline were identified using ICD-9-CM codes. Patients with a diagnosis of depression preceding their date of heart failure diagnosis were identified using ICD-9-CM codes 296.2, 296.3, 296.5, 300.4, 309.x, 311. Exposure to β-blocker therapy was extracted from outpatient pharmacy dispensing records. Patients were considered to be exposed to β-blockers if they filled at least one prescription for a β-blocker within 1 year of heart failure diagnosis. Exposure to other cardiac medications including statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and aldosterone antagonists was also extracted from outpatient pharmacy dispensing records.

Mortality data were extracted from a mortality data file with integrated death information derived from multiple sources including California state death master files, Social Security Administrative death master files, hospital deaths, and insurance enrollment records.

Baseline characteristics at time of index admission are presented as means with standard deviations, medians with interquartile ranges, or frequencies with percentages as appropriate. Differences in categorical data between patient groups were compared by Chi-square test. Differences in continuous data between patient groups were compared by Student's *t* tests or the Wilcoxon-Mann-Whitney test. Crude survival by β-blocker treatment was assessed with Kaplan-Meier analyses. Logistic regression was performed to examine the association between depression and treatment with β-blockers. Cox proportional hazard models were used to calculate the effect of β-blocker treatment on the risk of all-cause mortality. Proportional hazard assumption was tested using scaled Schoenfeld residuals. Hazard ratios were reported with 95% confidence intervals (CI). Statistical analyses were performed using STATA 14 (StataCorp, College Station, TX).

Results

From 2008 to 2014, we identified 16,557 patients diagnosed with heart failure who had echocardiogram information. Of these, 9,622 patients had a left ventricular ejection fraction of ≥50% and were excluded. Twenty patients were excluded because they had less than 7 days of follow-up information. The final study cohort consisted of 6,915 patients.

Of the 6,915 patients, 1,252 (18.1%) had a diagnosis of depression preceding their date of heart failure diagnosis. Baseline characteristics are shown in Table 1. Compared with patients without depression, patients with depression were older and more likely to be women. Co-morbidities of hypertension, dyslipidemia, diabetes mellitus, ischemic stroke, chronic obstructive pulmonary disease, and chronic kidney disease were more prevalent in the depression group.

Table 1
Baseline characteristics of the study population according to depression status

Variable	No depression (n = 5663)	Depression (n = 1252)	p Value
Age (years)	68.9 ± 14.0	70.1 ± 12.9	0.006
Male	3858 (68.1%)	634 (50.6%)	<0.001
White	2792 (49.3%)	720 (57.5%)	<0.001
Black	987 (17.4%)	156 (12.5%)	
Hispanic	1335 (23.6%)	304 (24.3%)	
Asian	488 (8.6%)	61 (4.9%)	
Other	61 (1.1%)	11 (0.9%)	
Hypertension	4568 (80.7%)	1076 (85.9%)	<0.001
Hyperlipidemia	3834 (67.7%)	931 (74.4%)	<0.001
Diabetes mellitus	2251 (39.8%)	559 (44.7%)	0.001
Obesity	1597 (28.2%)	403 (32.2%)	0.005
CAD	1844 (32.6%)	412 (32.9%)	0.81
Atrial fibrillation	1795 (31.7%)	416 (32.2%)	0.29
CVA/TIA	694 (12.3%)	228 (18.2%)	<0.001
CKD	2010 (35.5%)	498 (39.8)	0.004
COPD/Asthma	1758 (31.0%)	476 (38.0%)	<0.001
Diuretics	4388 (77.5%)	989 (79.0%)	0.25
Statin	4274 (75.5%)	934 (74.6%)	0.52
Beta-blockers	5150 (90.9%)	1100 (87.9%)	0.001
Ace-i/ARB	4767 (84.2%)	1020 (81.5%)	0.02
Aldo	1023 (18.1%)	230 (18.4%)	0.80
BNP (pg/ml)	681 (368, 1260)	643 (325, 1292)	0.09

Values are n (%), mean ± SD, or median (IQR).

CAD = coronary artery disease; CVA = cerebrovascular accident; TIA = transient ischemic attack; COPD = Chronic obstructive lung disease; CKD = chronic kidney disease. Ace-i = ace inhibitor; ARB = angiotensin-receptor blocker; Aldo = aldosterone antagonist. BNP = B-type natriuretic peptide.

BNP values available in 4,272 patients.

Patients with depression were less likely to be treated with β-blockers − 5,150 (90.9%) of patients without depression were treated with β-blockers, compared with 1,110 (87.9%) of patients with depression. No significant difference was observed in the use of diuretics, statins, or aldosterone antagonists. Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers was lower in the group with depression (84.2% vs 81.5%). Depression was associated with decreased odds of β-blocker treatment (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.59 to 0.87; p = 0.001) (Table 2). Even after adjusting for age, gender, ethnicity, medical co-morbidities and treatment with other cardiac medications, the association between depression and decreased odds of β-blocker treatment remained significant (OR 0.77, 95% CI 0.62 to 0.95, p = 0.016).

The total follow-up time was 18,094 person-years (mean follow-up time 2.6 years). During follow-up, 439 (35.1%) patients with depression died compared with 1,549 (27.4%) patients without depression.

Kaplan-Meier estimated survival estimates are shown in Figure 1. Higher mortality was observed in the group with depression (Figure 1). Patients were further stratified by β-blocker treatment. Patients treated with β-blockers had

Table 2
Univariate and multivariate analyses examining the association between depression and treatment with β blocker in patients with heart failure

Model	OR	95% CI	p Value
Univariate	0.72	0.59-0.87	0.001
Adjusted for age	0.74	0.61-0.90	0.002
Adjusted for age, gender and ethnicity	0.74	0.61-0.90	0.003
Adjusted for age, gender, ethnicity and comorbidities*	0.75	0.62-0.91	0.004
Adjusted for age, gender, ethnicity, comorbidities and treatment with other medications†	0.77	0.62-0.95	0.016

* Comorbidities: hypertension, hyperlipidemia, diabetes, obesity, coronary artery disease, atrial fibrillation, cerebrovascular accident, transient ischemic attack, chronic kidney disease, chronic obstructive pulmonary disease, and asthma.
† Medications: statin, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, aldosterone antagonist, and diuretics.

better survival, regardless of co-morbid depression. When treated with β-blockers, heart failure patients with depression had comparable survival compared with those without depression on β-blockers (Figure 1). Those who were not treated with β-blockers had worse survival than patients with no depression treated with β-blockers.

Cox-regression models were constructed to evaluate the association between depression, β-blocker treatment, and mortality (Table 3). Compared with patients without depression on β-blockers, patients with depression not treated with β-blockers had higher mortality (adjusted hazard ratio [HR], 1.4, 95% CI 1.09 to 1.7, p = 0.005). In contrast, patients with depression treated with β-blockers had significantly better survival compared with those not treated with β-blockers, with their survival comparable to patients without a prevalent diagnosis of depression (HR 1.1, 95% CI 0.97 to 1.2, p = 0.14).

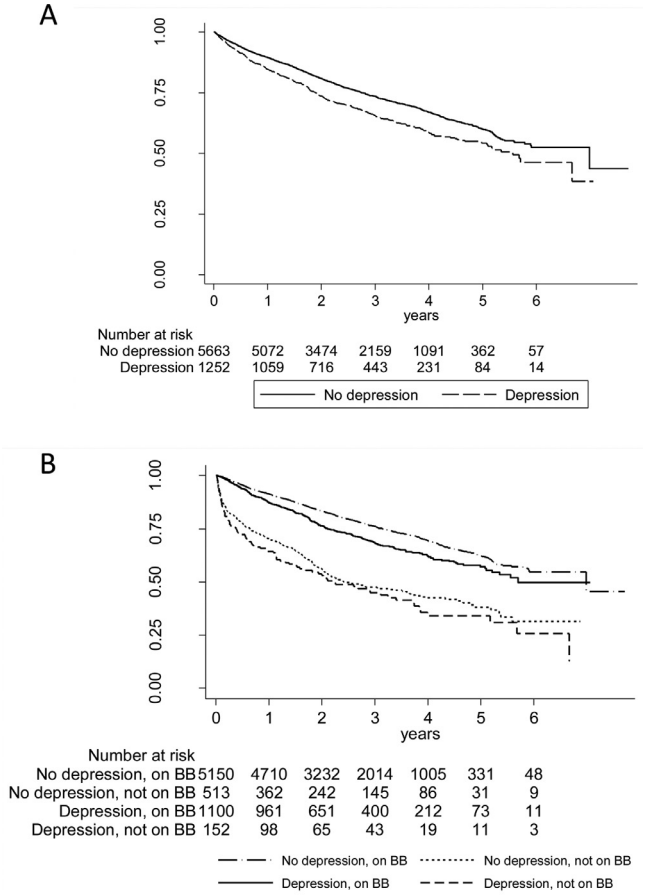

Figure 1. Kaplan-Meier survival estimates for all-cause mortality of heart failure patients (A) comparing patients with depression to patients without depression, log rank p <0.001. (B) Comparing four groups of patients (1) patients with depression treated with β-blockers (BB), (2) patients with depression not treated with β blockers, (3) patients without depression treated with β blockers, and (4) patients without depression not treated with β-blockers. Log rank p <0.001.

Discussion

In this study of patients with heart failure and depression, we found that β blocker utilization is lower among patients with co-morbid depression. Underutilization of β-blockers in heart failure patients is associated with worse survival. When patients with depression were treated with β-blockers, their survival was comparable to patients without depression, underscoring the importance of guidelines-directed medical therapy in this population.

Patients with cardiovascular disease have a high incidence of depression as well as higher morbidity, mortality, and readmission rates than patients without co-morbid psychiatric illnesses.[7-10] Depression and cardiovascular disease are closely linked, with the severity of depression correlating with the severity of cardiovascular disease.[11,12] Multiple inciting factors are posited as possibly playing a role in both, including socioeconomic factors such as increased prevalence of tobacco use and other toxin intake, physiologic mechanisms such as heightened inflammatory state due to depression, decreased heart rate variability, and impaired platelet function.[11-13] In addition, many psychotropic medications are known to have adverse effects on lipid profiles, diabetes, and cardiac function. Depression after MI or stroke has been known to have negative impacts on patient's quality of life, morbidity, and mortality.[9,14] Similar poor outcomes have been shown in patients with heart failure and depression.[15,16]

In this cohort of patients with heart failure, a significant proportion (18.1%) had co-morbid depression. Overall, these patients had worse outcomes compared with their nondepressed counterparts. Patients with depression had higher rates of cardiovascular risk factors including hypertension, dyslipidemia, and diabetes mellitus. These differences in baseline characteristics were also observed in other published cohorts.[17]

Guideline-directed medical therapy is underutilized in the group with depression. In particular, β-blocker therapy

Table 3
Hazard ratios of all-cause mortality in heart failure patients with and without depression

	Crude HR (95% CI)	p Value	Adjusted HR* (95% CI)	p Value	Adjusted HR† (95% CI)	p Value
No depression, treated with β-blockers	Reference		Reference		Reference	
No depression, not treated with β-blockers	1.6 (1.4-1.8)	<0.001	1.5 (1.3-1.7)	<0.001	1.3 (1.1-1.5)	0.001
Depression, treated with β-blockers	1.1 (0.99-1.3)	0.054	1.1 (0.99-1.3)	0.08	1.1 (0.97-1.2)	0.14
Depression, not treated with β-blockers	1.4 (1.2-1.8)	0.001	1.5 (1.2-1.9)	<0.001	1.4 (1.09-1.7)	0.005

* Adjusted for demographics (age, gender, race/ethnicity), and comorbidities including hypertension, hyperlipidemia, diabetes, obesity, coronary artery disease, atrial fibrillation, cerebrovascular accident, transient ischemic attack, chronic kidney disease, chronic obstructive pulmonary disease, and asthma.

† Adjusted for demographics, comorbidities and medications (statin, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, aldosterone antagonist, and diuretics).

is less commonly used in depressed patients compared with the nondepressed counterpart. There are several possible reasons for the difference in therapy for patients with heart failure alone and those with co-morbid depression. These include patient refusal or inability to reliably take medications, provider focus on the psychiatric illness at the expense of nonpsychiatric diagnoses, or provider bias. Some studies have shown that patients with cardiovascular disease and psychiatric illness are more likely to be treated at low quality cardiovascular disease centers and receive less patient education regarding condition and treatments.[15,18] Providers may also be concerned with medication interactions with psychotropic medications or the psychiatric illness itself. In addition, the regimens for heart failure are often complex, requiring frequent dosing, factors associated with decreased medication compliance further exacerbated by depression.[19]

Although the effect of β-blockers in depression has long been disputed, concerns over worsening mental health conditions may lead providers to undertreat cardiomyopathy. The concern that β-blocker therapy may worsen depression arose decades ago.[3,4] These reports studied propranolol, the most lipophilic and thus most centrally acting β-blocker, which is not part of guideline-directed medical therapies on cardiomyopathy and heart failure. Recent studies have shown that β-blocker use after acute myocardial infarction has not been associated with worsening symptoms of depression.[6,20-22] Nevertheless, continued concern of potential side effects may have contributed to the underutilization of β blockers in depressed patients.

Our study showed that underutilization of β blocker in depressed heart failure patients is associated with significantly worse survival. Most importantly, when patients with depression were treated with β-blockers, the increased mortality was no longer observed, and their survival was comparable to patients without depression. This observation suggests undertreatment with appropriate guideline-directed medical therapy as an important contributor to the worse outcomes in patients with depression.

Limitations of this study include a lack of depression severity scoring and New York Heart Association class of heart failure symptoms. Depression is a heterogeneous disease with severity that can vary from day to day. Ejection fraction also does not necessarily reflect functional capacity, which may be a more relevant metric when discussing the effects of depressed mood on quality of life. The observational nature of the study precludes conclusions regarding causation. Despite attempts to adjust for known confounders, residual confounding from unmeasured variables is possible. Furthermore, although survival improves with β-blocker therapy, the effect on depression was not evaluated in this study. The cohort studied was obtained from an insured population, and as such, may limit the generalizability to patients without insurance or those with limited access to medical care.

In conclusion, in this large contemporary population-based cohort, we found that β-blocker therapy remains underutilized in depressed heart failure patients. Underutilization of β-blocker therapy is associated with worse survival. Prognosis of depressed heart failure patients significantly improves and is comparable to nondepressed patients when guideline-directed medical therapy is used. Future research is needed to investigate the causes of undertreatment in patients with heart failure and co-morbid depression, and to explore strategies to improve utilization of guideline-directed medical therapy in depressed patients.

Disclosures

The author(s) has no conflicts of interest to disclose.

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. American College of Cardiology F. American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2013;62:e147–e239.
2. Bytyci I, Bajraktari G. Mortality in heart failure patients. *Anatol J Cardiol* 2015;15:63–68.
3. Avorn J, Everitt DE, Weiss S. Increased antidepressant use in patients prescribed beta-blockers. *JAMA* 1986;255:357–360.
4. Waal HJ. Propranolol-induced depression. *Br Med J* 1967;2:50.
5. Ranchord AM, Spertus JA, Buchanan DM, Gosch KL, Chan PS. Initiation of beta-blocker therapy and depression after acute myocardial infarction. *Am Heart J* 2016;174:37–42.
6. van Melle JP, Verbeek DE, van den Berg MP, Ormel J, van der Linde MR, de Jonge P. Beta-blockers and depression after myocardial infarction: a multicenter prospective study. *J Am Coll Cardiol* 2006;48:2209–2214.
7. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006;48:1527–1537.
8. Jiang W, Alexander J, Christopher E, Kuchibhatla M, Gaulden LH, Cuffe MS, Blazing MA, Davenport C, Califf RM, Krishnan RR, O'Connor CM. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch Intern Med* 2001;161:1849–1856.

9. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *Eur Heart J* 2014;35:1365–1372.
10. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* 2006;3:a42.
11. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 1998;55:580–592.
12. Shimbo D, Chaplin W, Crossman D, Haas D, Davidson KW. Role of depression and inflammation in incident coronary heart disease events. *Am J Cardiol* 2005;96:1016–1021.
13. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biol Psychiatry* 2010;67:1067–1074.
14. Vaccarino V, Badimon L, Bremner JD, Cenko E, Cubedo J, Dorobantu M, Duncker DJ, Koller A, Manfrini O, Milicic D, Padro T, Pries AR, Quyyumi AA, Tousoulis D, Trifunovic D, Vasiljevic Z, de Wit C, Bugiardini R, Reviewers ESCSDG. Depression and coronary heart disease: 2018 ESC position paper of the working group of coronary pathophysiology and microcirculation developed under the auspices of the ESC committee for practice guidelines. *Eur Heart J* 2019;0:1–15.
15. Albert NM, Fonarow GC, Abraham WT, Gheorghiade M, Greenberg BH, Nunez E, O'Connor CM, Stough WG, Yancy CW, Young JB. Depression and clinical outcomes in heart failure: an OPTIMIZE-HF analysis. *Am J Med* 2009;122:366–373.
16. Johnson TJ, Basu S, Pisani BA, Avery EF, Mendez JC, Calvin JE Jr., Powell LH. Depression predicts repeated heart failure hospitalizations. *J Card Fail* 2012;18:246–252.
17. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry* 2003;54:227–240.
18. Sayers SL, Hanrahan N, Kutney A, Clarke SP, Reis BF, Riegel B. Psychiatric comorbidity and greater hospitalization risk, longer length of stay, and higher hospitalization costs in older adults with heart failure. *J Am Geriatr Soc* 2007;55:1585–1591.
19. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000;160:2101–2107.
20. Freedland KE, Rich MW, Skala JA, Carney RM, Davila-Roman VG, Jaffe AS. Prevalence of depression in hospitalized patients with congestive heart failure. *Psychosom Med* 2003;65:119–128.
21. Carney RM, Rich MW, teVelde A, Saini J, Clark K, Freedland KE. Prevalence of major depressive disorder in patients receiving beta-blocker therapy versus other medications. *Am J Med* 1987;83:223–226.
22. Davis BR, Furberg CD, Williams CB. Survival analysis of adverse effects data in the beta-blocker heart attack trial. *Clin Pharmacol Ther* 1987;41:611–615.