Angiotensin Converting Enzyme Inhibitors and Beta-Blockers in African Americans with Heart Failure

Peter A. McCullough, MD, MPH; Edward F. Philbin, MD;
John A. Spertus, MD, MPH;
Keisha R. Sandberg, BS; Scott Kaatz, DO

Previous analyses have implied diminished efficacy of angiotensin converting enzyme inhibitors (ACEI), and equivalent or enhanced efficacy of beta-blockers (BB), in African Americans (AA) with congestive heart failure (CHF), when compared to placebo. These results may have been influenced by lead-time bias, in that AA may not have been entered into the older ACEI trials until late in their CHF course. Our goal was to use a prospective cohort study of 29,686 CHF patients within a single health system to examine the impact on AA mortality of administering ACEI and BB within the first year of CHF diagnosis. Pharmacy claims from 1995–1998 were available for 3353 newly diagnosed CHF patients (39.2% AA; $N=1317$) within the health maintenance organization. Rates of ACEI and BB use were 46.4% and 54.0%; 43.4% and 28.9%; and 40.7% and 18.6%, for Whites, AA, and other races, respectively. The relative risk reductions (RRR) for ACEI were 68.7%, $P<.0001$; 52.1%, $P<.0001$; and −36.3%, $P=.56$, for Whites, AA, and other races, respectively. The RRR for BB were 59.0%, $P<.0001$; 34.6%, $P=.009$; and 74.3%, $P=.17$, for Whites, AA, and other races, respectively. Age- and gender-adjusted survival rates for AA were significantly enhanced in those taking ACEI, BB, or a combination of the two: $P<.001$, $P=.001$, and $P=.003$, respectively. Although we could not control for selection bias, these data suggest that AA benefit from both ACEI and BB when treatment is initiated within the first year of CHF diagnosis. Future, similar analyses other databases should control for the duration of illness to avoid lead-time bias in AA with CHF. (*Ethn Dis*. 2003;13:331–336)

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From the Divisions of Cardiology, Nutrition, and Preventive Medicine, Willliam Beaumont Hospital, Royal Oak (PAM), Henry Ford Heart and Vascular Institute, Detroit (KRS), Department of Internal Medicine, Henry Ford Hospital, Detroit (SK), Michigan; Albany Medical College, Albany, New York (EFP); University of Missouri-Kansas City, Mid-America Heart Institute, Kansas City, Missouri (JAS).

Address correspondence and reprint requests to Peter A. McCullough, MD, MPH; Chief, Division of Nutrition and Preventive Medicine; William Beaumont Hospital, Beaumont Health Center; 4949 Coolidge; Royal Oak, MI 48073; 248-655-5900; 248-655-5901 (fax); pmc975@yahoo.com

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Introduction

Previous cross-sectional studies from large data sets have shown increases in the point prevalence of congestive heart failure (CHF) in the United States and Europe since the 1970s, with age, coronary artery disease, valvular disease, and poorly controlled hypertension found to be major determinants of CHF.[1–9] However, selection biases for entry into prospective cohort studies and randomized trials have limited the generalizability of these findings to community care due to an under-representation of African Americans (AA), women, and the elderly in the studies, and an under-utilization of pharmacotherapy by researchers.[10] Several recent small subgroup analyses of AA in clinical trials of angiotensin converting enzyme inhibitors (ACEI) and beta-blockers (BB) have reported conflicting findings as to the effects of using these treatments on hospitalization and mortality.[11–14] Clinicians and patients, alike, are somewhat confused about the expected benefits of these drugs, which have been demonstrated primarily in the Caucasian population. The purpose of the Resource Utilization Among Congestive Heart Failure (REACH) study was to report on the epidemiology of CHF, and its care patterns within an integrated health system.[15] The REACH study evaluated the extent of the initial diagnostic evaluation, and described patterns of proven pharmacotherapy utilization, with the goal of identifying opportunities for clinical improvement. This database, with its large AA component, was ideally suited for use in evaluating the impact of conventional therapies, including ACEI and BB, on all-cause survival.

Methods

Setting

The methods of the REACH study have been previously reported.[15] Briefly, Henry Ford Hospital is a 903-bed tertiary care center located in the Detroit metropolitan area, and receives patients whose care is provided primarily through the Henry Ford Health System (HFHS), a vertically integrated, mixed model managed care organization (MCO) which includes urban and suburban satellite clinics in Southeast Michigan.[16] Health Alliance Plan (HAP), the primary MCO for HFHS, maintains comprehensive administrative tables for encounters within HFHS and hospitals nationwide.

Case Definitions

An index case of CHF was defined as an individual who had accumulated at least 2 outpatient encounters (emergency department, urgent care, or clinic), or one hospitalization, coded for CHF during the study period from 1989 to 2000. This subgroup analysis is restricted to patients declared index cases between 1995 and 1998. As previously reported in REACH, approximately ⅔ of index cases were categorized

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as such due to one hospitalization, with the remaining third being defined as index cases after a second CHF outpatient encounter.[15] The 9th International Classification of Diseases, Clinical Modification (ICD-9-CM) codes for CHF used were previously validated in CHF case findings, and included the following: 428, 398.91, 402.01, 402.11, 402.91, 404.00, 404.01, 404.03, 404.10, 404.11, 404.13, 404.90, 404.91, 404.93, or hospitalizations identified as the diagnosis related-group (DRG) 127.[17–18] Validation of the CHF definition from chart notes has been previously reported.[15] The charts of a random sample of 263 REACH patients (44.1% women, 55.9% men) were reviewed. Of those undergoing chart review, 82.9% were confirmed to have CHF. Of those not having CHF explicitly listed in the chart, most had the cardiac substrate and associated findings to support the presence of CHF. Only 5.0% had no mention of cardiovascular disease in the chart notes. Death was ascertained in all study patients by death within a HFHS facility, death confirmed by State of Michigan Death Registry tapes, or by the National Center for Health Statistics Death Index.

Study Sample

From the parent database of 29,686 CHF patients, 3,353 HAP patients, who were continuously enrolled from 1995 to 1998, a period with complete pharmacy data, were selected for this sub-study. Drug exposures were taken if at least one prescription for the drug class was filled during the index year. The database was unable to provide more detailed information, such as specific drug within class, dose, quantity, or frequency of refills.

Statistical Analysis

Univariate statistics were reported as proportions, or means, and comparisons were made using chi-square, or analysis of variance, as appropriate. Multiple logistic regression was performed to identify the independent relations between demographics, diagnostic testing, and initial pharmacy claims on all-cause mortality. Survival analyses was carried out using the Cox proportional hazards model, allowing for age- and gender-adjusted survival, with age being recorded at the time of diagnosis. Statistical significance was chosen at the $\alpha < .05$ level.

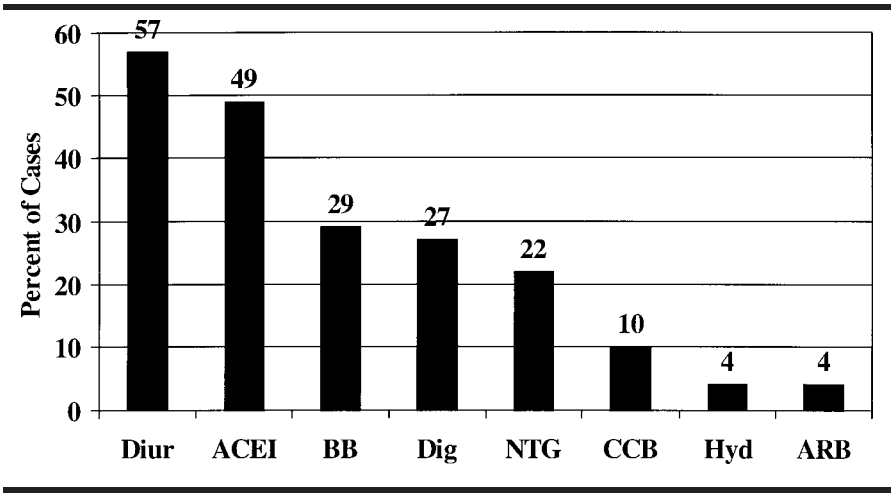

Fig 1. Overall rates of medication utilization during the first year of heart failure treatment in 3,353 HMO enrollees (all races) in the REACH Study. Diur=any form of diuretic; ACEI=angiotensin converting enzyme inhibitor; BB=beta-blocker; Dig=digoxin; NTG=long acting nitroglycerin; CCB=calcium channel blocker; Hyd=hydralazine; ARB=angiotensin II receptor blocker

RESULTS

Baseline Characteristics

The mean age was 68.0 ± 13.3 (20.7–103.0) years, and the sample population was 50.5% female. Racial proportions were as follows: White 57.4%, African-American 39.3%, and other races 3.3%. The "other" race group was comprised of women and men in the following categories: Hispanic, Native Americans, Asian, Middle-Eastern, and "unknown or unstated." The types of MCO plans were as follows: HMO alone, 56.7%; Medicare and HMO, 37.8%; and other combined HMO products, 5.5%. Forty-four percent of all cases were cardiologist-managed (defined as 2 or more visits within one year), with a mean age of 66.6 ± 12.8, and 55.8% of cases were managed by primary care physicians (PCP), with a mean age of 69.1 ± 13.5. Of note, if an ejection fraction (EF) of 45% was used to distinguish between systolic and diastolic dysfunction, 214/599 (35.7%) had predominately systolic dysfunction, with a mean EF=28.7 ± 9.4%, and 385/599 (64.3%) had predominately diastolic dysfunction, with a mean EF=55.7 ± 6.2%. Those patients with predominately systolic dysfunction were only slightly more likely to be cared for by a cardiologist (51.9%) than by a primary care physician (48.1%), $P=.01$.

Medication Profiling

Rates of medication utilization are given in Figure 1. Medication utilization

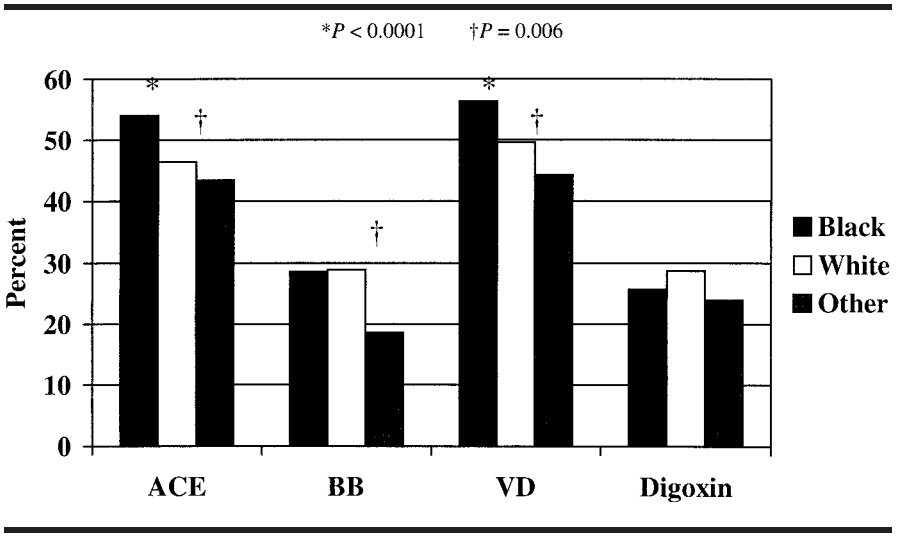

Fig 2. Rates of medication utilization per category according to race. ACE=angiotensin converting enzyme inhibitor; BB=beta-blocker; VD=angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, long-acting nitrates and hydralazine, or a combination of the three

patterns by demographic groups are presented in Figure 2. Categories of drug utilization are: 1) angiotensin converting enzyme inhibitor (ACEI); 2) beta-blocker (BB); 3) any vasodilator therapy (ACEI, combination of long acting nitrates and hydralazine, or an angiotensin II receptor blocker [ARB]); and 4) digoxin. Six hundred fifty seven patients (19.6%) received both an ACEI and BB. Of note, the data were collected prior to the release of most ARBs onto the US market. The database did not specify the primary reason for BB therapy; therefore, it was possible for BB therapy to be prescribed primarily for ischemic heart disease in patients who had concomitant CHF.

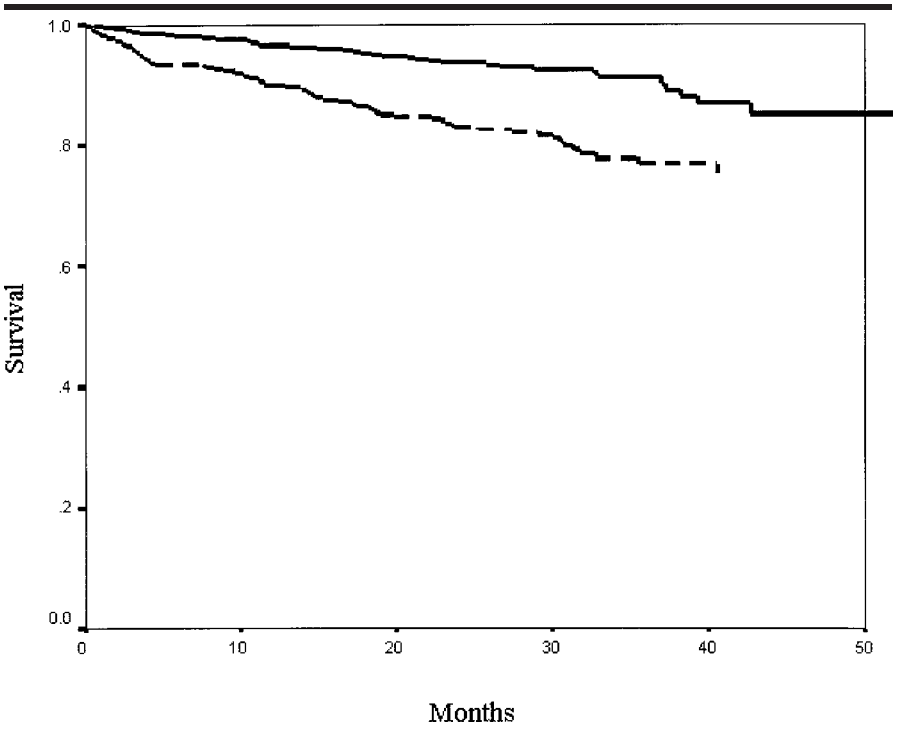

Fig 3. Age and gender adjusted survival for 1317 AA prescribed ACEI in the first year of CHF, *P*<.0001 for survival benefit with ACEI (solid line) versus those not on ACEI (broken line)

Medications and Survival in African Americans

Figure 3 displays the all-cause, age- and gender-adjusted survival in the AA subgroup of 1317 patients who were prescribed ACEI in the first year of diagnosis. Likewise, Figures 4 and 5 display the effects of BB, and a combination of ACEI and BB, on adjusted all-cause survival. Of note, within the AA subgroup, the rates of medication usage for ACEI, BB, and the combination of ACEI and BB were 711 (54.0%), 377 (28.6%), and 270 (20.5%), respectively.

Initial Package of Care

Multivariate analysis confirmed age, OR=1.024, 95% CI 1.015–1.033, *P*<.001; male gender, OR=1.33, 95% CI 1.08–1.64, *P*=.007; use of vasodilators (ACEI, ARB, or combination of hydralazine and long-acting nitrates), OR=0.52, 95% CI 0.41–0.64, *P*<.0001; use of BB, OR=0.75, 95% CI 0.57–0.98, *P*=.04; and cardiologist care, OR=0.51, 95% CI 0.42–0.67, *P*<.0001, as independent predictors of mortality (Hosmer Lemeshow statistic, *P*=.50). Of note, the multivariate analysis did not include payer source, since all patients in this analysis were members of the same HMO.

DISCUSSION

Efforts to implement CHF guidelines and to utilize mortality-reducing drugs may be affecting the population of CHF patients in several ways.[19–20] The methods used in the REACH study

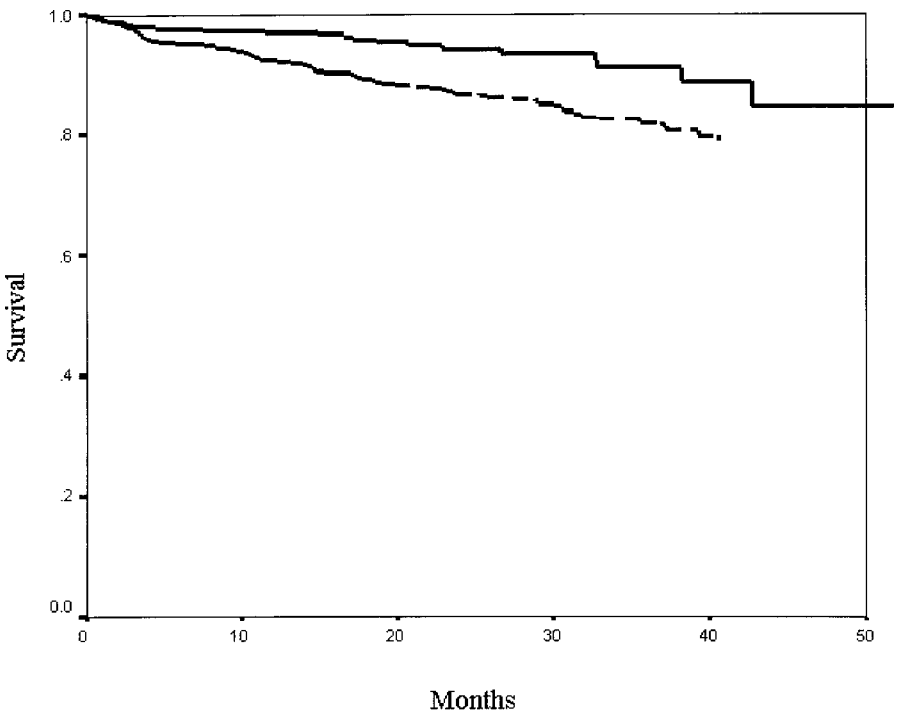

Fig 4. Age and gender adjusted survival for 1317 AA prescribed BB in the first year of CHF, *P*=.001 for survival benefit with BB (solid line) versus those not on BB (broken line)

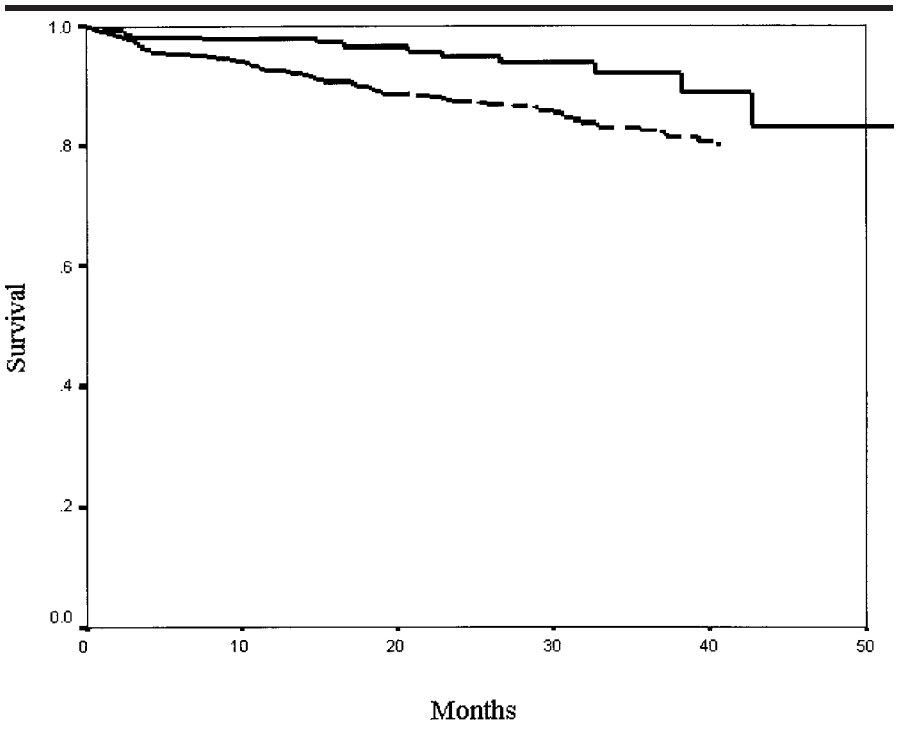

Fig 5. Age and gender adjusted survival for 1317 AA prescribed both ACEI and BB (solid line) in the first year of CHF, *P*=.003 for survival benefit with both compared to all others not on both ACEI and BB

Our study demonstrated that, when access to care is equal, AA CHF patients are as likely, if not more likely, to receive life-prolonging medications.

have proved to correspond with other population estimates of CHF survivorship, supporting the case that improved treatment of CHF prolongs the survival of these patients.[10–24] Although the underlying etiologies of CHF in REACH are unknown, we would expect to find, as with other CHF populations, the leading cause of CHF to be ischemic heart disease.[25]

Our medication profiling data are consistent with those published by others through the 90s.[26] Less than optimal use of ACEI and BB has been the rule in outcomes studies, despite randomized trials supporting their widespread use.[27–29] Our study demonstrated that when access to care is equal, AA CHF patients are as likely, if not more likely, to receive life-prolonging medications. This may be due, in part, to expected higher rates of diabetes and hypertension among AA not captured in our database. The multivariate analysis clearly demonstrated that efficacious medications predicted from clinical trials have an early independent benefit, with respect to all-cause mortality in CHF populations.

Of particular importance, our study demonstrated a clear age- and gender-adjusted survival advantage of using ACEI, BB, and the combination of ACEI and BB, in the 1317 patients of the AA subgroup. This contradicts findings from 800 AA patients, as reported by the Studies of Left Ventricular Function database, and from 180 AA males studied in the second Vasodilator-Heart Failure Trial (V-HEFT II); neither of

these studies found any measurable benefits of using ACEI in AA.[11–12] With respect to BB on AA CHF survival, our results are consistent with those reported by Yancy and coworkers from the US Carvedilol Heart Failure Trials Program, which studied 217 AA receiving carvedilol vs placebo, and found the use of BB beneficial with respect to both hospitalizations and mortality.[13] However, the Beta-Blocker Evaluation of Survival Trial (BEST) database was evaluated, and reported no benefit from using bucindolol in the overall population, or in the subgroup of 318 AA.[14] Importantly, these small subgroup analyses from clinical trials may have been misleading to clinicians who could mistakenly construe a differential response to therapy as a lack of therapeutic efficacy among AA. The size of our AA population, equal access to care, and evaluation from the first year of diagnosis, are factors that have helped clarify the benefit of using these commonly accepted forms of therapy in AA. Importantly, ACEI and BB are recommended as standard therapies for the treatment of CHF in all patients, including AA.[30]

We acknowledge that there are multiple limitations to our study. Using ICD-9-CM codes as the basis for defining CHF is not comparable to the stringent definitions used in Framingham, NHANES, or other studies; therefore, a misclassification bias may exist.[31] This bias is almost certainly non-differential, and would bias any analytic conclusion to the null hypothesis of testing or treatment comparisons. The limitations of our study, which utilized administrative, clinical, and pharmacy claims data, stem from multiple assumptions. For instance, while we assumed that the CHF was a recent condition, being newly diagnosed, it could have existed for years, simply eluding capture by the database techniques utilized. In addition, we assumed medications were specifically prescribed for CHF, but acknowledge that they could have been prescribed for other conditions, including ischemic heart disease or hypertension. Lastly, we assumed that pharmacy claims reflected actual use of the medications by patients, with no way of assessing actual patient compliance. In addition, we did not have important medical co-morbidity data, such as the presence of chronic renal disease, which could influence short and long-term survival.[32] However, we believe that our findings can be helpful in understanding aspects of CHF populations and their management, but cannot be generalized to the individual, or to his or her physician's treatment plan. We fully acknowledge that large-scale, properly designed clinical trials, which include adequate numbers of African-American patients, are needed to definitively assess the safety and efficacy of heart failure therapy in this population.

CONCLUSIONS

We conclude that use of ICD-9-CM codes and automated sources of data provide multiple opportunities for improvement in the initial management of CHF. Although under-utilized, the early introduction of treatment with ACEI and BB appears to indicate high quality care and improved outcomes. Among the AA subgroup, there was an observed mortality benefit in those for whom ACEI, BB, or the combination, was prescribed.

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AUTHOR CONTRIBUTIONS

Design and concept of study: McCullough, Philbin, Spertus
Acquisition of data: McCullough, Philbin, Kaatz
Data analysis and interpretation: McCullough, Sandberg, Kaatz
Manuscript draft: McCullough, Sandberg
Statistical expertise: McCullough, Philbin
Acquisition of funding: McCullough
Administrative, technical, or material assistance: McCullough, Philbin, Sandberg
Supervision: McCullough, Philbin