Does aspirin use adversely influence intermediate-term postdischarge outcomes for hospitalized patients who are treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers? Findings from Organized Program to Facilitate Life-Saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF)

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Background Conflicting data exist regarding a potential deleterious association between aspirin (ASA) and angiotensin-converting enzyme inhibitors (ACEIs) when used concurrently in patients with heart failure (HF). How such an interaction may be influenced by underlying etiology of HF and whether it extends to patients treated with angiotensin receptor blockers (ARBs), however, are not known.

Methods Eligible patients from the OPTIMIZE-HF registry were dichotomized into those with ischemic or nonischemic HF. Potential associations between ASA and ACEI or ARB use and 60- to 90-day postdischarge outcomes were assessed using Cox proportional and logistic regression modeling. Models were adjusted for factors known to influence the outcome of interest and by propensity score for ACEI or ARB prescription after an index HF admission.

Results Mortality was not increased (hazard ratio [95% CI]) when ASA was used in conjunction with ACEI (0.51 [0.29-0.87]) or ARB (0.29 [0.09-0.96]) in patients with ischemic or nonischemic (ACEI 0.71 [0.42-1.21], ARB 1.42 [0.74-2.74]) HF. Regression model parameter estimates trended toward harm reduction, but interaction terms for mortality and a composite of mortality or rehospitalization were nonsignificant (*P* for all >.05).

Conclusions When combined with ACEI or ARB, ASA had no demonstrable adverse effect on intermediate-term postdischarge outcomes for patients with ischemic or nonischemic HF. (Am Heart J 2010;159:222-30.e2.)

Aspirin (ASA) and angiotensin-converting enzyme inhibitors (ACEIs) are frequently used in patients with heart failure (HF). Several animal and human studies, however, have reported a potential deleterious association when these 2 agents are used in conjunction.[1-7] The mechanism for this hypothesized adverse interaction is thought to involve disparate effects at the prostaglandin level, with ASA causing an attenuation of ACEI-mediated bradykinin potentiation.[7-10] Theoretical consequences of this include a reduction of bradykinin-induced systemic arterial vasodilatation and a loss of beneficial bradykinin-related cardiac remodeling effect

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Table I. Predictor variables included in multivariable analyses

Mortality model
Admission SBP, per 10–mm Hg increase, up to 140 mm Hg
Admission SCr <4 mg/dL, per unit increase, up to 4 mg/dL
Age, per 10-y increase
History of pulmonary reactive airway disease
Admission weight (per 10-kg increase)
Lower extremity edema
Discharge medications—lipid-lowering agent
Sodium, per 1-U increase, up to 140 mEq/L
History of depression
Discharge SBP, per 10–mm Hg increase, up to 130 mm Hg
Liver disease
Admission SBP, per 10–mm Hg increase, >140 mm Hg
Discharge medications—any β-blocker
Propensity score for ACEI or ARB use at discharge
Composite model
Admission hemoglobin (up to 11 g/dL)
Admission SCr up to and including 3.8 mg/dL
Admission SCr >3.8 mg/dL
Admission medications—diuretic
History of pulmonary disease (COPD, reactive airway disease)
>0 HF hospitalizations in past 6 m
Admission medications—nitrates
Admission medications—digoxin
History of CVA/TIA
Admission SBP (in increments of 10 mm Hg)
Coronary angiography performed during hospitalization
Mechanical ventilation performed during hospitalization
AICD placed during hospitalization
Discharge medication—lipid-lowering agent
History of liver disease
Left ventricular systolic dysfunction
Propensity score for ACEI or ARB use at discharge

SBP, Systolic blood pressure; *SCr*, serum creatinine; *COPD*, chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *TIA*, transient ischemic attack; *AICD*, automatic implantable cardioverter defibrillator.

Table II. Input variables included in final propensity score model

Primary cause of admission—HF
Admission characterization of HF—pulmonary congestion
Other conditions for HF—noncompliance with medications
Admission symptom—palpitations
White
Peripheral vascular disease
Renal disorder
No known HF before this admission
Rales
Admission medications
Any β-blocker
ACEI
Aldosterone antagonist
ARB
Digoxin
Diuretic
Diastolic blood pressure (10 mm Hg)
Admission hemoglobin (in g/dL)
Age <70 y
Heart beat ≥120 beat/min
Admission serum creatinine up to 4 mg/dL
Coronary angiography performed during hospitalization
Dialysis performed during hospitalization
Left ventricular assist device placed during hospitalization
Pacemaker placed during hospitalization
Right cardiac catheterization performed during hospitalization

by ACE inhibition, both of which may be magnified in patients with HF who often have up-regulation of bradykinin receptors.[8] Nonetheless, whether these effects impart a clinically important detriment remains a matter of controversy.[11-15]

Angiotensin receptor blockers (ARBs) have emerged in the past decade as an alternative to ACEIs for management of patients with hypertension and HF.[16-18] Although ARBs produce a hemodynamic effect similar to ACEIs, they do so independent of the bradykinin pathway. It would seem, therefore, that ARBs are less likely to be affected by concurrent ASA therapy; but published data on the interaction (if any) between these agents are nonexistent.

To address this uncertainty, we sought to investigate the effect of ASA on intermediate-term (60- to 90-day postdischarge) outcomes for patients hospitalized with acute HF who are treated with ACEIs or ARBs. Because existing evidence strongly supports the use of ASA in patients with underlying coronary artery disease (CAD) or ischemic heart disease,[19-22] we divided, a priori, our study population into 2 cohorts based on documented etiology of HF (ischemic vs nonischemic).

Methods

Study design

This study was designed as a retrospective analysis of the Organized Program to Facilitate Life-Saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry. The rationale and design of OPTIMIZE-HF have been discussed in detail elsewhere.[23] In brief, OPTIMIZE-HF was a performance improvement program for patients hospitalized with HF. Using uniform case ascertainment methodology,[23,24] OPTIMIZE-HF compiled a comprehensive database of important characteristics (demographic, pathophysiologic, and clinical), treatment patterns, and outcomes for 48,612 hospitalized patients with HF. Data collection was monitored and coordinated independent of the registry sponsor (GlaxoSmithKline, Philadelphia, PA) by Outcome Sciences, Inc (Cambridge, MA). A prespecified 10% of the total OPTIMIZE-HF population was selected for 60- to 90-day follow-up, and incident data on mortality and rehospitalization were prospectively collected. Baseline characteristics and outcomes for the follow-up population (n = 5,791) have been previously described.[24]

Each participating center (n = 259) was required to have institutional review board approval of the OPTIMIZE-HF protocol before study initiation. For hospitals that participated in follow-up data collection (n = 91), written informed consent was mandatory. Because this present study examined previously collected deidentified data, approval was granted by the Wayne State University School of Medicine (Detroit, MI) Human Investigations Committee with exemption from full board review.

Table III. Baseline characteristics for the overall study population, the ischemic cohort, and the nonischemic cohort

	Overall study population	Ischemic cohort	Nonischemic cohort
No. of patients (%)	5701	2411 (42.3)	3290 (57.7)
Mean age, y (SD)	72.0 (13.8)	73.7 (11.3)	70.8 (15.2)
Female, n (%)	2782 (48.8)	961 (39.9)	1821 (55.3)
White, n (%)	4446 (78.0)	2051 (85.1)	2395 (72.8)
Black, n (%)	1040 (18.2)	283 (11.8)	757 (23.2)
Hispanic, n (%)	113 (2.0)	56 (2.3)	57 (1.7)
Mean LVEF, % (SD)	36.9 (17.0)	33.7 (15.2)	39.5 (17.9)
LVEF <40%, n (% of those with LVEF assessed)	2592 (57.0)	1346 (65.6)	1246 (50.0)
Hospitalized for HF in prior 6 m, n (%)	1681 (36.5)	842 (41.8)	839 (32.4)
Type 2 diabetes mellitus, n (%)	1481 (26.0)	689 (28.6)	792 (24.1)
Type 1 diabetes mellitus, n (%)	951 (16.7)	471 (19.5)	480 (14.6)
History of CAD/ischemic heart disease, n (%)	2848 (50.0)	1933 (80.2)	915 (27.8)
Hyperlipidemia, n (%)	2259 (39.6)	1174 (48.7)	1085 (33.0)
Atrial arrhythmia, n (%)	1192 (33.5)	833 (34.5)	1079 (31.9)
COPD, n (%)	1741 (30.5)	692 (28.7)	1049 (31.9)
Reactive airway disease, n (%)	484 (8.5)	113 (4.7)	371 (11.3)
Smoker within past year, n (%)	1041 (18.9)	413 (17.8)	628 (19.7)
Chronic kidney disease, n (%)	1154 (20.2)	504 (20.9)	650 (19.8)
Peripheral vascular disease, n (%)	903 (15.8)	440 (18.2)	463 (14.1)
Hypertension, n (%)	4111 (72.1)	1680 (69.7)	2431 (73.9)
Depression, n (%)	773 (13.6)	269 (11.2)	504 (15.3)
Liver disease, n (%)	126 (2.2)	32 (1.3)	94 (2.9)
Thyroid abnormality, n (%)	950 (16.7)	387 (16.1)	563 (17.1)
History of prior CVA/TIA, n (%)	874 (15.3)	401 (16.6)	473 (14.4)
Admission rales, n (%)	3467 (62.1)	1506 (63.9)	1961 (60.7)
Admission lower extremity edema, n (%)	3629 (65.1)	1511 (64.3)	2118 (65.6)
Mean admission SBP, mm Hg (SD)	140.9 (32.2)	136.2 (30.3)	144.4 (33.2)
Median admission SCr, mg/dL (IQR)	1.3 (1.0, 1.8)	1.4 (1.1, 1.8)	1.2 (1.0, 1.7)
Mean admission Hgb, g/dL (SD)	12.2 (2.1)	12.1 (2.0)	12.3 (2.1)
Mean admission sodium, mEq/L (SD)	137.6 (4.6)	137.7 (4.7)	137.6 (4.5)
Median admission BNP, pg/mL (IQR)	815.0 (424.0, 1700.0)	946.0 (484.6, 2030.0)	733.5 (381.0, 1490.0)
Median admission troponin, ng/mL (IQR)	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)
Median admission weight, kg (IQR)	80.0 (66.0, 97.5)	80.0 (67.1, 96.1)	80.0 (65.3, 98.4)
Median weight change, kg (IQR)	−1.8 (−4.5, 0.0)	−2.0 (−4.5, 0.0)	−1.8 (−4.5, 0.0)
Admission β-blocker, n (%)	3113 (54.6)	1520 (63.0)	1593 (48.4)
Admission ACEI, n (%)	2372 (41.6)	1100 (45.6)	1272 (38.7)
Admission ARB, n (%)	706 (12.4)	293 (12.2)	413 (12.6)
Admission diuretic, n (%)	3885 (68.1)	1752 (72.7)	2133 (64.8)
Admission digoxin, n (%)	1395 (24.5)	672 (27.9)	723 (22.0)
Admission statin, n (%)	2079 (36.5)	1187 (49.2)	892 (27.1)
Mean discharge SBP, mm Hg (SD)	123.9 (22.4)	121.8 (22.0)	125.4 (22.5)
Median discharge BNP, pg/dL (IQR)	575.5 (296.0, 1180.0)	667.5 (357.5, 1390.0)	504.0 (258.2, 1067.0)
Discharge β-blocker, n (%)	3847 (67.9)	1711 (71.4)	2136 (65.3)
Discharge diuretic, n (%)	4687 (82.2)	2012 (83.5)	2675 (81.3)
Discharge digoxin, n (%)	1701 (29.9)	766 (31.8)	936 (28.4)
Discharge statin, n (%)	2232 (39.2)	1346 (55.8)	964 (29.3)

COPD, Chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *TIA*, transient ischemic attack; *SBP*, systolic blood pressure; *SCr*, serum creatinine; *IQR*, interquartile range; *Hgb*, hemoglobin; *BNP*, B-type natriuretic peptide.

Study population

This analysis focused on patients >18 years of age who participated in follow-up data collection, survived to hospital discharge without transfer to another short-term hospital or hospice, were not enrolled in a clinical trial testing alternatives to ACEIs as first-line therapy, and did not have contra-indications to ACEI or ARBs at discharge (n = 5,701). Within this pool, patients were dichotomized by documented HF etiology into ischemic (n = 2,411) and nonischemic (n = 3,290) cohorts. Six subgroups were then formulated within each cohort based on discharge medications as follows: no ASA, ACEI, or ARB; ASA only; ACEI only; ARB only; ASA plus ACEI; and ASA plus ARB. Because of limited representation in both the ischemic (n = 40) and nonischemic (n = 69) cohorts, patients discharged on all 3 medications (ie, ASA, ACEI, and ARB) or a combination of ACEI and ARB without ASA were excluded from the final analysis.

Outcome measures

Outcomes of interest were death and a composite of death or rehospitalization within 90 days of discharge from the hospital after an episode of acute decompensated HF. To avoid the issue of competing risk, rehospitalization was not considered as an individual outcome.

Statistical analysis

Descriptive analyses were performed for the overall study population and ischemic/nonischemic cohorts. Relevant data are reported by mean with SD or median with interquartile range for continuous variables and percentages of nonmissing values for categorical variables. Within each cohort, patient characteristics and treatments were compared across predefined subgroups using Pearson χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables. Heart failure medication use and contraindications or intolerance were assessed at discharge from the index hospital stay and during follow-up.

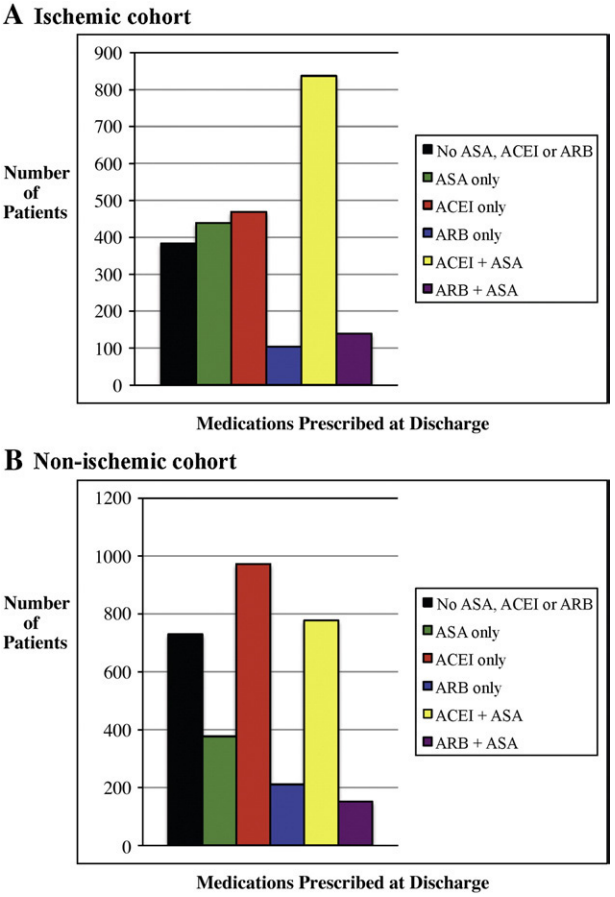
Unadjusted analyses were performed in 3 groups based on discharge medications as follows: patients on ASA only, patients on ACEIs only, and patients on ARBs only. Unadjusted Kaplan-Meier survival curves were derived, and the log-rank test was used to compare the survival distribution among groups. The numbers at risk are included to indicate the completeness of follow-up through 90 days. The results of the univariate analysis are presented as hazard ratio (HR) with corresponding 95% CI for the mortality model and odds ratio (OR) with 95% CI for the composite model.

Adjusted analyses were performed using Cox proportional hazards regression models for postdischarge death and logistic regression models for the combination of postdischarge death and rehospitalization (as date of event was not available). For modeling purposes, discharge use of ASA, ACEIs, or ARBs (as 3 main effects) and interactions between any of 2 medications were forced into previously derived and validated OPTIMIZE-HF models of mortality and a composite of mortality or rehospitalization (Table I).[24] Patients with missing data for model covariates were excluded from adjusted analyses. Comparison between patients included (mortality = 4,732 [83%], composite = 3,784 [66.4%]) and excluded (mortality = 969 [17%], composite = 1,917 [33.6%]) in multivariable modeling revealed no significant differences in baseline characteristics or outcomes (data not shown). Results of multivariable analysis are presented as HR with corresponding 95% CI for the mortality model and OR with 95% CI for the composite model.

Propensity score analysis was performed to account for potential medication selection bias. The linearity assumption for continuous measures was evaluated using restricted cubic spline transformations. When needed, appropriate transformations such as piecewise linear splines were applied. A *P* value of .05 was used for both entry and retention in the final propensity score model (Table II), and the propensity score was included as a covariate in mortality and composite models. In addition, the general estimating equation was used to account for within-hospital clustering of characteristics in both models; and sensitivity analysis was conducted to explore the impact of ACEI or ARB eligibility on observed medication effects. The correlation within hospital was taken into account with the use of robust-sandwich standard error estimate for the regression coefficients in models. SAS version 8.2 (SAS Institute Inc, Cary, NC) was used for all statistical analyses.

All analyses were performed independently by the Duke Clinical Research Institute (Durham, NC), and no extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, the drafting and editing of the paper, and its final contents. All authors have read and agree to the manuscript as written.

Figure 1



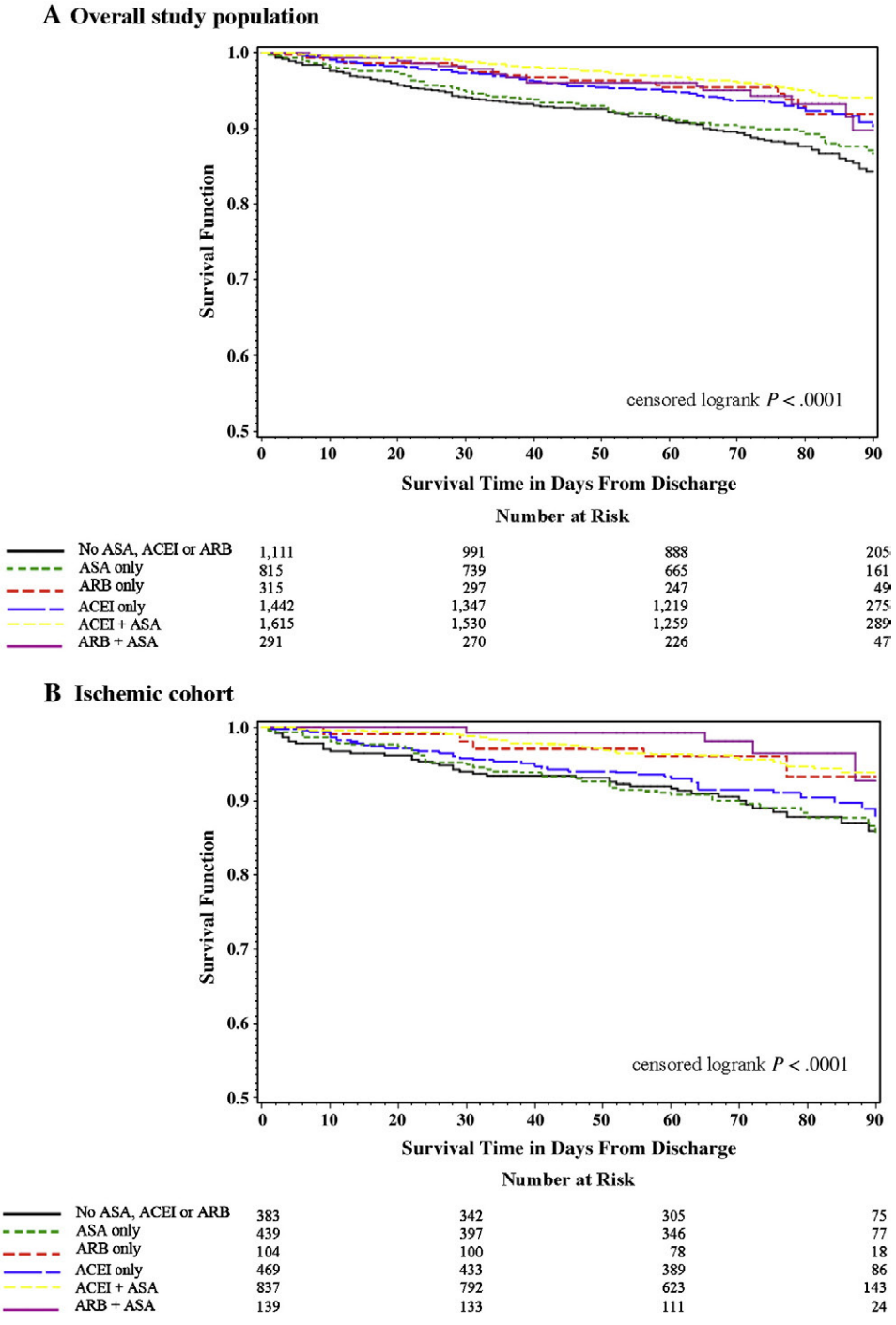
A and **B**, Marginal distribution of discharge medications for (**A**) ischemic and (**B**) nonischemic.

Results

Patient characteristics

Baseline characteristics for the overall study population (n = 5,701) as well as the ischemic (n = 2,411) and the nonischemic (n = 3,290) cohorts are presented in Table III. In general, patients with ischemic HF were slightly older (mean age 73.7 ± 11.3 vs 70.8 ± 15.2 years); less likely to be female (39.9% vs 55.3%) or black (11.8% vs 23.2%); and more likely to have CAD/ischemic heart disease (80.2% vs 27.8%), diabetes mellitus (combined type 1 and type 2 48.1% vs 38.7%), or hyperlipidemia (48.7% vs 33.0%) than those with a nonischemic etiology. Patients with ischemic HF were also more frequently hospitalized in the preceding 6 months for HF (41.8% vs 32.4%), less hypertensive on admission (mean systolic blood pressure 136.2 ± 30.3 vs 144.4 ± 33.2 mm Hg), and

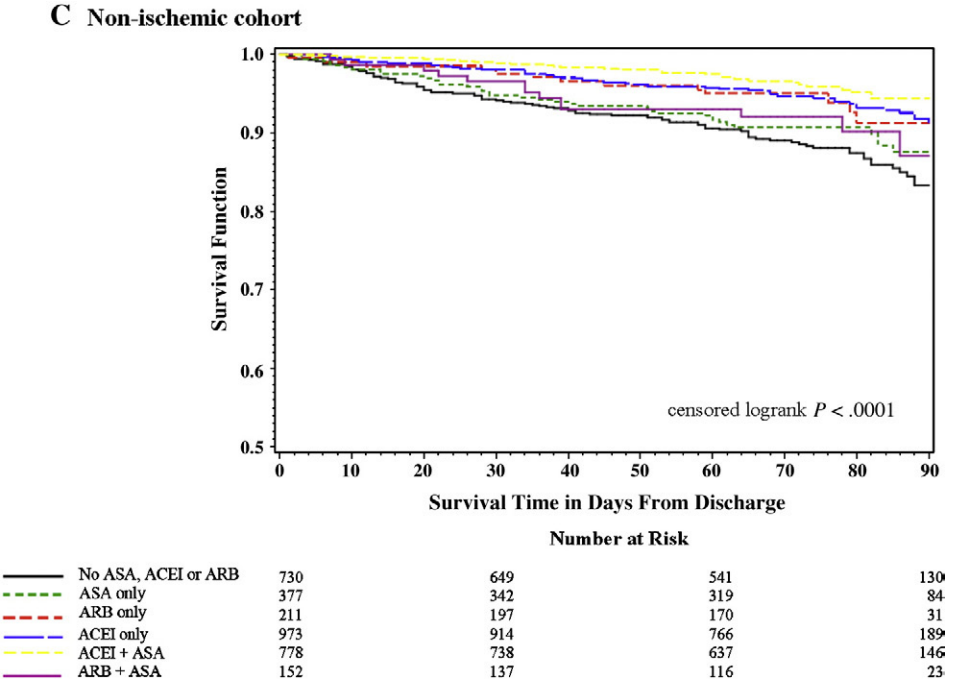
Figure 2



A to **C**, Kaplan-Meier curves depicting survival by subgroup for (**A**) the overall study population, (**B**) the ischemic cohort, and (**C**) the nonischemic cohort.

more frequently on a β-blocker or statin therapy on admission (63.0% vs 48.8% and 49.2% vs 27.1%, respectively) and at discharge (71.4% vs 65.3% and 52.6% vs 29.3%, respectively). In addition, patients with ischemic HF had a lower mean (SD) left ventricular ejection fraction (LVEF) than those with nonischemic

Figure 2 (continued)



disease (33.7% [15.2] vs 39.5% [17.9]); and a greater proportion (65.6% vs 50.0%) had left ventricular systolic dysfunction (LVSD, defined as LVEF <40%).

Marginal distribution of medication use at discharge for the ischemic and nonischemic cohorts is presented in Figure 1, *A* and *B*. Most patients in the ischemic cohort were discharged on combination therapy with ACEI and ASA (n = 837, 35.3%), whereas in the nonischemic cohort, monotherapy with ACEI was most common (n = 973, 30.2%). A relatively high proportion of patients in the ischemic (n = 383, 16.1%) and nonischemic (n = 730, 22.7%) cohorts, however, were discharged without prescription for ASA, ACEI, or ARB.

Baseline characteristics for patients who received ACEI alone, ARB alone, ACEI plus ASA, and ARB plus ASA by cohort are presented in Tables IV and V in an accompanying online supplement. Statistically significant intergroup differences existed for patients within both cohorts for a number of variables including age; LVEF; smoking status; history of atrial arrhythmia, chronic kidney disease, or peripheral vascular disease; admission serum creatinine, hemoglobin, and sodium; body weight; use of ACEI, ARB, or statins; and discharge use of β-blockers, diuretics, or statins.

Mortality model

A total of 2,018 patients (84.0%) in the ischemic cohort and 2,714 (82.4%) in the nonischemic cohort were eligible for inclusion in mortality models. Among these patients, 343 (7.2%) deaths occurred during the follow-up period, with relatively equal distribution between the ischemic (n = 141, 7.0%) and the nonischemic (n = 202, 7.4%) cohorts. Overall and by cohort, survival was lowest for patients who were not prescribed ASA, ACEIs, or ARBs at discharge (unadjusted Kaplan-Meier curves provided in Figure 2, *A-C*). For patients with ischemic HF, unadjusted hazard of mortality was lower (HR [95% CI]) with individual use of all 3 medications at the time of hospital discharge (ACEI 0.55 [0.39-0.77], ARB 0.35 [0.17-0.72], and ASA 0.70 [0.50-0.96]); but in those with a nonischemic etiology, only ACEI appeared to confer benefit (ACEI 0.46 [0.34-0.62], ARB 0.82 [0.61-1.10], and ASA 0.78 [0.51-1.18]).

After multivariable adjustment, neither ACEI nor ARB (as individual factors without ASA) had any clear effect on mortality in both ischemic (1.04 [0.62-1.75] and 0.62 [0.24-1.59]) and nonischemic (0.77 [0.51-1.16] and 0.88 [0.49-1.58]) cohorts. For ischemic patients, ASA combined with ACEI (0.51 [0.29-0.87]) or ARB (0.29 [0.09-0.96]) appeared to provide some measure of hazard reduction; but the interaction parameter estimates (ACEI and ASA −0.72 [*P* = .09], ARB and ASA −0.75 [*P* = .33]) did not achieve statistical significance. For nonischemic patients, the addition of ASA to ACEI (0.71 [0.42-1.21]) or ARB (1.42 [0.74-2.74]) therapy did not appear to increase or decrease hazard; but again, the interaction

parameter estimates were not statistically significant (ACEI and ASA −0.08 [P = .74], ARB and ASA −0.48 [P = .22]).

Composite model

Fewer patients in the ischemic (1,706 [71.1%]) and nonischemic (2,078 [63.2%]) cohorts were eligible for inclusion in composite outcome analysis. A total of 1,397 (36.9%) events occurred in these patients, with similar rates in the ischemic (38.9%, n = 664) and nonischemic (35.3%, n = 733) cohorts. Unadjusted risk (OR [95% CI]) of the composite outcome was lower in both ischemic and nonischemic patients with HF who received ACEIs (0.65 [0.53-0.80] and 0.62 [0.51-0.75]) or ARBs (0.60 [0.43-0.85] and 0.67 [0.50-0.90]) at discharge but not ASA (0.93 [0.76-1.14] and 0.96 [0.80-1.16]).

On multivariable modeling, odds of the composite outcome remained lower in ischemic patients who received ACEI (0.72 [0.55-0.96]) and ARB (0.71 [0.51-1.00]) at discharge but not ASA (1.03 [0.85-1.25]). In nonischemic patients, the direction and relative magnitude of the univariate association between all 3 medications and outcome were unchanged (ACEI 0.70 [0.54-0.90], ARB 0.70 [0.54-0.92], and ASA 0.98 [0.84-1.15]). For both cohorts, there was no statistical evidence of an interaction between ASA and ACEI (P [ischemic] = .18 and P [nonischemic] = .63) or ARB (P [ischemic] = .12 and P [nonischemic] = .76).

Discussion

In this study of the OPTIMIZE-HF registry, ASA use did not adversely influence 60- to 90-day outcomes for patients hospitalized with acute HF who were prescribed concurrent ACEI or ARB therapy at discharge. For postdischarge mortality, the addition of ASA actually trended towards benefit; but as evidenced by the width of related CIs, our analysis was probably underpowered to examine this interaction as a 2-sided occurrence. These findings extended to all patients with HF irrespective of underlying etiology (ischemic or nonischemic) and were independent of potential interhospital variability or propensity for ACEI or ARB use at discharge.

Results of this study support the notion that in actual clinical practice ASA does not appear to exert a deleterious effect on outcomes associated with ACEI in patients with HF, but the existence of contradictory data renders the issue a matter of ongoing debate. In the Studies of Left Ventricular Dysfunction trial, for example, a reduction in the expected individual contributory survival benefit from both enalapril and ASA was found when the 2 medications were used in combination.[1] A subsequent meta-analysis, however, combining the Studies of Left Ventricular Dysfunction data with the results of 5 other long-term randomized clinical trials of ACEIs found no evidence of an interaction between ASA and ACEI (P = .07) and a clear reduction in risk of major clinical outcomes for patients who received ASA at baseline (OR 0.80 [99% CI 0.73-0.88]) and those who did not (OR 0.71 [99% CI 0.62-0.81]).[25] More recently, 2 clinical trials that prospectively evaluated antithrombotic therapy in patients with HF (The Warfarin/Aspirin Study in Heart Failure[26] and The Warfarin and Antiplatelet Therapy in Chronic Heart Failure[27] trials) reported an increase in HF admissions among individuals who received ASA.

Of importance, these studies were all clinical trials conducted in an outpatient setting with chronic HF patients who had LVSD. Because our data were derived from a registry that included all patients with HF rather than those who meet stringent inclusion and exclusion criteria, they are more likely to reflect the general population and, consequently, real-world outcomes. Although OPTIMIZE-HF did not collect data beyond the intermediate-term (60 to 90 days) postdischarge period, our results are remarkably consistent with recently published findings from the Enhanced Feedback for Effective Cardiac Treatment study, which noted that, among patients (n = 7,352, 56% with an ischemic etiology) discharged after a first hospitalization for HF, users of ACEIs were less likely to die or require HF readmission in the ensuing year than nonusers, even if they were receiving ASA.[28] The absence of an interaction between ASA and ACEIs was persistent in a number of subgroups including patients who had no history of CAD. This, combined with data from the National Heart Care Project, which showed no attenuation of benefit in Medicare patients with CAD discharged on ACEI and ASA after hospitalization for acute HF,[29] supports the consistency we found in apparent lack of interaction across HF etiologies.

Potential adverse effects of ASA when used in conjunction with ARBs have been less well investigated and remain poorly defined. Because of pharmacologic properties that differ from ACEIs; however, one would expect a lower likelihood of interaction; and our study shows that, for intermediate-term outcomes, this is indeed true. The only other existing data come from a subgroup analysis of the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity study that reported no modification of the beneficial effects of candesartan on cardiovascular death or HF rehospitalization by ASA over 37.7 months of follow-up.[30] Similar to our study, outcomes did not differ based on etiology of HF or by LVEF, indicating that combined treatment with ASA and ARBs can be considered with limited concern for interaction in a broad range of patients with HF.

Study limitations

Our study was subject to several important limitations. Although follow-up patients in OPTIMIZE-HF were identified prospectively, ASA use was not randomly

assigned. Consequently, our results should not be viewed as reflective of an adequately powered clinical trial and cannot be interpreted as definitive evidence of a cause-and-effect relationship. In addition, despite covariate adjustment for a number of factors including LVSD and propensity matching, other measured or unmeasured variables may have influenced observed clinical outcomes. Among these, patient compliance with prescribed medications, prescribed duration and dosing of medications at discharge, and untracked alterations in outpatient therapy (especially ASA, ACEI, or ARB dose adjustments) may be particularly important. Furthermore, although we did account for potential variability in hospital characteristics and clustering of events using the general estimating equation, applicability of these data is limited to facilities that are similar to participating OPTIMIZE-HF institutions (described elsewhere[24]). Lastly, 90-day outcomes may not capture potential drug effects on cardiac remodeling and chronic hemodynamics, both of which may impact protracted morbidity and mortality for patients with HF.

Conclusions

Data from this study of a broad cohort of patients with HF from all regions of the country suggest that use of ASA is not associated with a statistically significant adverse effect on intermediate-term postdischarge outcomes when combined with ACEI or ARB therapy in either ischemic or nonischemic patients with HF.

Disclosures

The OPTIMIZE-HF registry was funded by GlaxoSmithKline, Philadelphia, PA.

Gregg C. Fonarow, MD, reported that he has served as a consultant for GlaxoSmithKline (modest) and received honorarium from GlaxoSmithKline (significant).

References

1. Al-Khadra AS, Salem DN, Rand WM, et al. Antiplatelet agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial. J Am Coll Cardiol 1998; 31:419-25.
2. Minshall RD, Tan F, Nakamura F, et al. Potentiation of the actions of bradykinin by angiotensin I–converting enzyme inhibitors. The role of expressed human bradykinin B2 receptors and angiotensin I–converting enzyme in CHO cells. Circ Res 1997;81:848-56.
3. Nguyen KN, Aursnes I, Kjekshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). Am J Cardiol 1997;79:115-9.
4. Pellacani A, Brunner HR, Nussberger J. Plasma kinins increase after angiotensin-converting enzyme inhibition in human subjects. Clin Sci (Lond) 1994;87:567-74.
5. Spaulding C, Charbonnier B, Cohen-Solal A, et al. Acute hemodynamic interaction of aspirin and ticlopidine with enalapril: results of a double-blind, randomized comparative trial. Circulation 1998;98: 757-65.
6. Peterson JG, Topol EJ, Sapp SK, et al. Evaluation of the effects of aspirin combined with angiotensin-converting enzyme inhibitors in patients with coronary artery disease. Am J Med 2000;109: 371-7.
7. Meune C, Mourad JJ, Bergmann JF, et al. Interaction between cyclooxygenase and the renin-angiotensin-aldosterone system: rationale and clinical relevance. J Renin Angiotensin Aldosterone Syst 2003;4:149-54.
8. Emanueli C, Maestri R, Corradi D, et al. Dilated and failing cardiomyopathy in bradykinin B(2) receptor knockout mice. Circulation 1999;100:2359-65.
9. Meune C, Mahe I, Mourad JJ, et al. Aspirin alters arterial function in patients with chronic heart failure treated with ACE inhibitors: a dose-mediated deleterious effect. Eur J Heart Fail 2003;5:271-9.
10. Schror K. Role of prostaglandins in the cardiovascular effects of bradykinin and angiotensin-converting enzyme inhibitors. J Cardiovasc Pharmacol 1992;20(Suppl 9):S68-73.
11. Brunner-La Rocca HP. Interaction of angiotensin-converting enzyme inhibition and aspirin in congestive heart failure: long controversy finally resolved? Chest 2003;124:1192-4.
12. Hall D. Controversies in heart failure. Are beneficial effects of angiotensin-converting enzyme inhibitors attenuated by aspirin in patients with heart failure? Cardiol Clin 2001;19:597-603.
13. Konstam MA. Aspirin and heart failure: square evidence meets a round patient. Congest Heart Fail 2003;9:203-5.
14. Massie BM. Aspirin use in chronic heart failure: what should we recommend to the practitioner? J Am Coll Cardiol 2005;46:963-6.
15. Takkouche B, Etminan M, Caamano F, et al. Interaction between aspirin and ACE Inhibitors: resolving discrepancies using a meta-analysis. Drug Saf 2002;25:373-8.
16. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-6.
17. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582-7.
18. Willenheimer R, Helmers C, Pantev E, et al. Safety and efficacy of valsartan versus enalapril in heart failure patients. Int J Cardiol 2002; 85:261-70.
19. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993; 342:821-8.
20. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782-8.
21. Swedberg K, Held P, Kjekshus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med 1992; 327:678-84.
22. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-53.
23. Fonarow GC, Abraham WT, Albert NM, et al. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart

Failure (OPTIMIZE-HF): rationale and design. Am Heart J 2004; 148:43-51.
24. O'Connor CM, Abraham WT, Albert NM, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J 2008;156:662-73.
25. Teo KK, Yusuf S, Pfeffer M, et al. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. Lancet 2002;360: 1037-43.
26. Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J 2004;148: 157-64.
27. Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. Circulation 2009;119:1616-24.
28. McAlister FA, Ghali WA, Gong Y, et al. Aspirin use and outcomes in a community-based cohort of 7352 patients discharged after first hospitalization for heart failure. Circulation 2006;113: 2572-8.
29. Masoudi FA, Wolfe P, Havranek EP, et al. Aspirin use in older patients with heart failure and coronary artery disease: national prescription patterns and relationship with outcomes. J Am Coll Cardiol 2005;46: 955-62.
30. Chang S, Kosolcharoen P, Murray D, et al. Lack of interaction between angiotensin receptor blocker and aspirin in patients with heart failure. Circulation 2006;114:II_767.

Appendix A. Online supplement

Table IV. Baseline characteristics for the ischemic cohort by subgroup

	ACEI only	ARB only	ACEI + ASA	ARB + ASA	*P*
No. of patients (% overall)	469 (19.8)	104 (4.4)	837 (35.3)	139 (5.9)	
Mean age, y (SD)	73.2 (11.7)	75.1 (10.8)	72.7 (11.5)	73.9 (10.0)	.002
Female, n (%)	186 (39.7)	51 (49.0)	325 (38.8)	62 (54.3)	.231
White, n (%)	391 (85.2)	89 (87.3)	676 (83.6)	119 (87.5)	.164
Black, n (%)	57 (12.2)	13 (12.6)	115 (13.9)	14 (10.2)	.063
Hispanic, n (%)	9 (1.9)	2 (1.9)	21 (2.5)	2 (1.4)	.813
Mean LVEF, % (SD)	32.1 (14.3)	35.0 (14.2)	31.6 (14.2)	35.8 (17.3)	<.001
LVEF <40%, n (% of those with LVEF assessed)	276 (68.1)	48 (60.0)	553 (73.8)	71 (61.9)	<.001
Hospitalized for HF in prior 6 m, n (%)	161 (40.8)	30 (36.1)	293 (41.9)	46 (40.7)	.656
Type 2 diabetes mellitus, n (%)	137 (29.2)	33 (31.7)	250 (29.9)	41 (29.5)	.636
Type 1 diabetes mellitus, n (%)	78 (16.6)	18 (17.3)	159 (19.0)	35 (25.2)	.156
History of CAD/ischemic heart disease, n (%)	366 (78.0)	85 (81.7)	677 (80.9)	118 (84.9)	.114
Hyperlipidemia, n (%)	233 (49.7)	51 (49.0)	408 (48.7)	76 (54.7)	.644
Atrial arrhythmia, n (%)	208 (44.3)	43 (41.3)	239 (28.6)	42 (30.2)	<.001
COPD, n (%)	131 (27.9)	26 (25.0)	213 (25.4)	35 (25.2)	.006
Reactive airway disease, n (%)	27 (5.8)	7 (6.7)	32 (3.8)	10 (7.2)	.341
Smoker within past year, n (%)	92 (20.4)	14 (14.0)	175 (21.7)	13 (9.8)	<.001
Chronic kidney disease, n (%)	68 (14.5)	20 (19.2)	113 (13.5)	30 (21.6)	<.001
Peripheral vascular disease, n (%)	81 (17.3)	18 (17.3)	141 (16.8)	23 (16.5)	.248
Hypertension, n (%)	333 (71.0)	72 (69.2)	601 (71.8)	107 (139)	.07
Depression, n (%)	46 (9.8)	14 (13.5)	92 (11.0)	17 (12.2)	.490
Liver disease, n (%)	5 (1.1)	1 (1.0)	9 (1.1)	3 (2.2)	.672
Thyroid abnormality, n (%)	73 (15.6)	19 (18.3)	116 (13.9)	30 (21.6)	.163
History of prior CVA/TIA, n (%)	67 (14.3)	18 (17.3)	150 (17.9)	21 (15.1)	.627
Admission rales, n (%)	288 (63.0)	71 (68.9)	533 (64.8)	90 (65.2)	.787
Admission lower extremity edema, n (%)	293 (64.4)	67 (66.3)	532 (65.0)	87 (64.0)	.991
Mean admission SBP, mm Hg (SD)	136.1 (31.1)	139.3 (30.7)	136.0 (28.9)	140.5 (33.0)	.064
Median admission SCr, mg/dL (IQR)	1.3 (1.0, 1.7)	1.4 (1.1, 1.8)	1.2 (1.0, 1.6)	1.4 (1.1, 1.8)	<.001
Mean admission Hgb, g/dL (SD)	12.2 (2.1)	11.8 (2.2)	12.3 (2.0)	12.2 (2.0)	.002
Mean admission sodium, mEq/L (SD)	137.8 (4.5)	137.7 (4.9)	138.2 (4.0)	137.9 (4.6)	.003
Median admission BNP, pg/mL (IQR)	907.0 (516.0, 1,850.0)	886.0 (518.0, 1,640.0)	939.0 (518.0, 2,130.0)	797.0 (437.0, 1,570.0)	.417
Median admission troponin, ng/mL (IQR)	0.2 (0.1, 0.4)	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)	.098
Median admission weight, kg (IQR)	82.1 (66.0, 96.6)	84.0 (67.8, 95.2)	83.6 (67.1, 97.5)	87.3 (71.0, 100.0)	.031
Median weight change, kg (IQR)	−2.0 (−4.1, 0.0)	−1.8 (−4.1, 0.0)	−2.0 (−5.0, 0.0)	−2.0 (−4.1, −0.5)	.805
Admission β-blocker, n (%)	291 (62.0)	65 (62.5)	544 (65.0)	94 (67.6)	.160
Admission ACEI, n (%)	331 (70.6)	7 (6.7)	582 (69.5)	7 (5.0)	<.001
Admission ARB, n (%)	15 (3.2)	79 (76.0)	15 (1.8)	101 (72.7)	<.001
Admission diuretic, n (%)	358 (76.3)	78 (75.0)	591 (70.6)	102 (73.4)	.383
Admission digoxin, n (%)	159 (33.9)	37 (35.6)	224 (26.8)	34 (24.5)	.008
Admission statin, n (%)	216 (46.1)	50 (48.1)	437 (52.2)	78 (56.1)	.057
Mean discharge SBP, mm Hg (SD)	120.8 (21.6)	123.9 (23.0)	120.7 (21.8)	124.0 (21.6)	.080
Median discharge BNP, pg/dL (IQR)	618.0 (329.4, 1,270.0)	585.0 (297.0, 1,190.0)	628.4 (382.0, 1,290.0)	600.0 (292.0, 848.0)	.168
Discharge β-blocker, n (%)	332 (71.1)	71 (68.9)	659 (78.9)	98 (70.5)	<.001
Discharge diuretic, n (%)	404 (86.1)	90 (86.5)	721 (86.1)	122 (87.8)	<.001
Discharge digoxin, n (%)	177 (37.7)	40 (38.5)	285 (34.1)	32 (23.0)	<.001
Discharge statin, n (%)	225 (48.0)	53 (51.0)	481 (57.5)	86 (61.9)	<.001

COPD, Chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *TIA*, transient ischemic attack; *SBP*, systolic blood pressure; *SCr*, serum creatinine; *IQR*, interquartile range; *Hgb*, hemoglobin; *BNP*, B-type natriuretic peptide.

Table V. Baseline characteristics for the nonischemic cohort by subgroup

	ACEI only	ARB only	ACEI + ASA	ARB + ASA	*P*
No. of patients (% overall)	973 (30.2)	211 (6.6)	778 (24.2)	152 (4.7)	
Mean age, y (SD)	68.3 (16.1)	71.7 (14.5)	69.6 (15.0)	71.8 (13.3)	<.001
Female, n (%)	520 (53.4)	124 (58.8)	393 (50.5)	89 (58.6)	.005
White, n (%)	671 (71.7)	145 (73.2)	509 (67.1)	107 (73.8)	<.001
Black, n (%)	244 (25.4)	46 (22.2)	227 (29.3)	32 (21.2)	<.001
Hispanic, n (%)	16 (1.6)	5 (2.4)	16 (2.1)	2 (1.3)	.879
Mean LVEF, % (SD)	36.6 (17.5)	41.9 (18.2)	36.3 (17.70	40.1 (16.8)	<.001
LVEF <40%, n (% of those with LVEF assessed)	436 (56.9)	67 (45.9)	372 (58.9)	61 (50.4)	<.001
Hospitalized for HF in prior 6 m, n (%)	236 (30.7)	53 (31.0)	190 (30.8)	43 (36.4)	.544
Type 2 diabetes mellitus, n (%)	238 (24.5)	57 (27.0)	189 (24.3)	42 (27.6)	.045
Type 1 diabetes mellitus, n (%)	127 (13.1)	34 (16.1)	107 (13.8)	30 (19.7)	.324
History of CAD/ischemic heart disease, n (%)	253 (26.0)	53 (25.1)	229 (29.4)	55 (36.2)	<.001
Hyperlipidemia, n (%)	324 (33.3)	78 (37.0)	275 (35.3)	64 (42.1)	.001
Atrial arrhythmia, n (%)	326 (33.5)	92 (43.6)	180 (23.1)	46 (30.3)	<.001
COPD, n (%)	298 (30.6)	73 (34.6)	221 (28.4)	45 (29.6)	.057
Reactive airway disease, n (%)	115 (11.8)	27 (12.8)	86 (11.1)	19 (12.5)	.756
Smoker within past year, n (%)	199 (21.1)	34 (17.2)	179 (23.6)	27 (18.5)	.004
Chronic kidney disease, n (%)	165 (17.0)	43 (20.4)	99 (12.7)	34 (22.4)	<.001
Peripheral vascular disease, n (%)	121 (12.4)	38 (18.0)	93 (12.0)	30 (19.7)	.007
Hypertension, n (%)	711 (73.1)	175 (82.9)	593 (76.2)	129 (84.9)	<.001
Depression, n (%)	134 (13.8)	38 (18.0)	108 (13.9)	30 (19.7)	.165
Liver disease, n (%)	24 (2.5)	0 (0.0)	22 (2.8)	3 (2.0)	.007
Thyroid abnormality, n (%)	158 (16.2)	43 (20.4)	110 (14.1)	23 (15.1)	.031
History of prior CVA/TIA, n (%)	133 (13.7)	38 (18.0)	109 (14.0)	31 (20.4)	.029
Admission rales, n (%)	575 (60.1)	140 (68.3)	486 (63.5)	85 (56.7)	.002
Admission lower extremity edema, n (%)	637 (66.8)	135 (64.0)	496 (65.3)	97 (65.5)	.797
Mean admission SBP, mm Hg (SD)	145.2 (34.4)	146.7 (31.6)	147.6 (32.4)	146.7 (31.6)	<.001
Median admission SCr, mg/dL (IQR)	1.2 (1.0, 1.6)	1.3 (1.0, 1.8)	1.2 (0.9, 1.5)	1.3 (1.1, 1.9)	<.001
Mean admission Hgb, g/dL (SD)	12.5 (2.2)	12.1 (2.0)	12.5 (2.0)	12.2 (1.9)	<.001
Mean admission sodium, mEq/L (SD)	137.7 (4.3)	137.3 (4.8)	138.1 (4.4)	137.1 (4.6)	<.001
Median admission BNP, pg/mL (IQR)	729 (368.0, 1,520.0)	633.5 (393.0, 1,260.0)	806.0 (435.0, 1,540.0)	754.5 (359.9, 1,760.0)	.008
Median admission troponin, ng/mL (IQR)	0.2 (0.1, 0.3)	0.3 (0.1, 0.5)	0.2 (0.1, 0.4)	0.2 (0.0, 0.3)	.018
Median admission weight, kg (IQR)	81.2 (66.2, 101.1)	81.0 (64.9, 102.0)	81.2 (66.0, 99.0)	80.9 (64.4, 100.7)	.009
Median weight change, kg (IQR)	−1.8 (−4.5, 0.0)	−1.8 (−4.1, 0.0)	−2.0 (−5.0, 0.0)	−1.8 (−3.6, 0.0)	.330
Admission β-blocker, n (%)	485 (49.8)	111 (52.6)	367 (47.2)	88 (57.9)	.009
Admission ACEI, n (%)	614 (63.1)	20 (9.5)	430 (55.3)	13 (8.6)	<.001
Admission ARB, n (%)	16 (1.6)	150 (71.1)	25 (5.1)	113 (74.2)	<.001
Admission diuretic, n (%)	630 (64.7)	163 (77.3)	474 (60.9)	106 (69.7)	<.001
Admission digoxin, n (%)	217 (22.3)	46 (21.8)	158 (20.3)	30 (19.7)	.244
Admission statin, n (%)	243 (25.0)	61 (28.9)	238 (30.6)	55 (36.2)	<.001
Mean discharge SBP, mm Hg (SD)	124.7 (22.6)	127.7 (23.5)	125.5 (22.0)	126.7 (21.9)	.112
Median discharge BNP, pg/dL (IQR)	458.0 (244.0, 994.0)	525.5 (293.0, 998.0)	499.0 (288.0, 1000.0)	786.5 (370.0, 1,180.0)	.107
Discharge β-blocker, n (%)	683 (70.3)	141 (66.8)	568 (73.1)	114 (75.0)	<.001
Discharge diuretic, n (%)	819 (84.2)	189 (89.6)	671 (86.2)	132 (86.8)	<.001
Discharge digoxin, n (%)	299 (30.7)	65 (30.8)	227 (29.2)	37 (24.3)	.231
Discharge statin, n (%)	253 (26.0)	61 (28.9)	300 (38.6)	59 (38.8)	<.001

COPD, Chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *TIA*, transient ischemic attack; *SBP*, systolic blood pressure; *SCr*, serum creatinine; *IQR*, interquartile range; *Hgb*, hemoglobin; *BNP*, B-type natriuretic peptide.