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FOCUS ISSUE: ASPIRIN

Aspirin Use in Older Patients With Heart Failure and Coronary Artery Disease

National Prescription Patterns and Relationship With Outcomes

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OBJECTIVES We sought to determine patterns of aspirin use and the relationship between aspirin prescription and outcomes in patients with coronary artery disease (CAD) and heart failure (HF).

BACKGROUND Because of the potential for exacerbating hypertension or renal insufficiency and possible interactions with angiotensin-converting enzyme (ACE) inhibitors, the use of aspirin for secondary prevention of coronary events is controversial in patients with HF.

METHODS We studied a national sample of Medicare beneficiaries ≥65 years old after hospitalization for HF with CAD and without aspirin contraindications between April 1998 and June 2001. We assessed factors associated with aspirin prescription and the relationship between aspirin and outcomes in regression models accounting for differences in patient, physician, and hospital characteristics and for clustering of patients by hospital.

RESULTS Of the 24,012 patients, 54% received aspirin. Treated patients had lower unadjusted rates of death (31% vs. 39% for those not receiving aspirin, $p < 0.001$). In multivariable analyses, aspirin remained associated with a lower risk of death (risk ratio [RR] 0.94; 95% confidence interval [CI] 0.90 to 0.99). This association was similar regardless of hypertension, renal insufficiency, or treatment with ACE inhibitors (p for all interactions > 0.2). Aspirin also was associated with lower risks of death or all-cause readmission (RR 0.98; 95% CI 0.97 to 0.99) and of death or readmission for HF (RR 0.98; 95% CI 0.96 to 0.99).

CONCLUSIONS Almost one-half of patients with CAD hospitalized for HF in the U.S. are not treated with aspirin. This study found no evidence of harm from aspirin in this population and suggests a treatment benefit. Withholding aspirin based upon theoretical concerns about adverse effects appears to be unjustified. (J Am Coll Cardiol 2005;46:955–62) © 2005 by the American College of Cardiology Foundation

Aspirin is an inexpensive and effective treatment for many patients with coronary artery disease (CAD). Although clinical practice guidelines advocate the use of aspirin for patients with acute coronary syndromes (1,2), previous revascularization (3), and chronic angina (4), its use in patients with CAD and concomitant heart failure is controversial. Physiological data suggest the possibility of an antagonistic effect between aspirin and angiotensin-converting enzyme (ACE) inhibitors (5). Furthermore, aspirin can exacerbate hypertension and renal insufficiency, potentially worsening heart failure (6–8). Existing data assessing the effects of aspirin on outcomes in patients with heart failure from post-hoc analyses of randomized trials and observational studies are conflicting (9–18).

Although patterns of aspirin prescription in patients with primary CAD diagnoses have been examined in detail (19–23), those in patients with CAD and heart failure are not well described. Current heart failure treatment guide-

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CAD = coronary artery disease
CI = confidence interval
GFR = glomerular filtration rate
LV = left ventricular
NHC = National Heart Care
MI = myocardial infarction
RR = risk ratio
SCr = serum creatinine

lines, although noting the potential limitations of aspirin, consider the use of antiplatelet agents for patients with underlying CAD a level IIa recommendation (i.e., one for which the weight of evidence is in favor of use despite conflicting evidence) (24). The lack of consistent supporting evidence and a corresponding class I indication for the use of aspirin in these patients may result in variable rates of use of a potentially beneficial medication.

We therefore sought to study aspirin prescription in a contemporary national cohort of older Medicare beneficiaries with heart failure and coexisting CAD. Our goal was to characterize national patterns of aspirin use in this population and to determine the relationship between aspirin prescription and the outcomes of mortality and readmission at one year. The study of this large high-risk cohort represents a unique opportunity to assess both the patterns of use and the potential benefit of aspirin in patients with both conditions.

METHODS

Study sample. The patient cohort in this study is derived from the National Heart Care (NHC) Project, a Centers for Medicare and Medicaid Services project to improve the quality of heart failure care for Medicare beneficiaries (25). The project database contains detailed demographic and clinical data on 78,882 fee-for-service Medicare beneficiaries hospitalized with the principal discharge diagnosis of heart failure between April 1998 and March 1999 or July 2000 and June 2001, inclusive. Medicare administrative bills for hospitalization were searched for International Classification of Diseases, Ninth Revision, Clinical Modification codes 428.x, 402.01, 402.11, 402.91, 404.01, 404.11, and 404.9 to identify hospitalizations primarily for heart failure. Records were excluded if the patient was transferred to another acute care facility, left against medical advice, or had chronic renal failure requiring dialysis. After these selection criteria were applied, as many as 800 records were selected for abstraction from each state, Puerto Rico, and the District of Columbia. In states in which fewer than the targeted number of heart failure discharges occurred during the sampling period, a complete census of discharges was obtained. In cases in which more than one hospitalization for heart failure was identified for a particular patient, only one of the discharges was selected randomly for inclusion in the study cohort.

We restricted our study cohort to those subjects with CAD. Because this study was of medical therapy at hospital discharge, patients who died during the index hospitalization were excluded (n = 5,048). Because patients younger than 65 years that are enrolled in Medicare qualify as the result of special circumstances (chronic disability or end-stage renal disease), we limited the study cohort to subjects age 65 years and older. Patients with a contraindication to aspirin use were excluded from the analysis (n = 7,516). Aspirin was considered at least relatively contraindicated in patients with hematocrit values <30%, platelet counts <100,000/ml, or with secondary diagnosis International Classification of Diseases, Ninth Revision, Clinical Modification codes for "coagulation defects" (286.x), "gastrointestinal hemorrhage" (456.0 to 456.2, 459.0, 530.7, 530.8, 531.0-531.4, 531.6, 532.0 to 532.4, 532.6, 533.0 to 533.4, 533.6, 534.0 to 534.4, 534.6, 569.3, 578.x) or "purpura and other hemorrhagic conditions" (287.x). Finally, because this study focused upon aspirin use and drug interactions specific to aspirin, patients treated with warfarin or nonaspirin antiplatelet agents at hospital discharge (n = 11,660), regardless of aspirin prescription, were excluded. The final analysis sample contained 24,012 discharges.

Data. PATIENT CHARACTERISTICS. Identified charts were forwarded to clinical data abstraction centers, where trained medical record reviewers collected data for 195 variables. Abstracted elements included demographic characteristics, past cardiac and noncardiac history, patient characteristics on hospital admission, laboratory values, and events during the index hospitalization, including procedures. For the purposes of quantifying renal function, the serum creatinine (SCr) closest to hospital discharge was used. Because serum creatinine does not accurately reflect renal function in many elderly patients, estimated glomerular filtration rate (GFR) was calculated using the abbreviated Modification of Diet in Renal Disease Study Equation: estimated GFR = $186 \times (\mathrm{SCr})^{-1.154} \times (\mathrm{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$ (26). Because <5% of the cohort had an estimated GFR >89 ml/min/1.73 m^2, this variable was categorized as >59 ml/min/1.73 m^2 (National Kidney Foundation categories of normal-mild renal insufficiency), 30 to 59 ml/min/1.73 m^2 (moderate renal insufficiency), and <30 ml/min/1.73 m^2 (severe renal insufficiency).

PHYSICIAN AND HOSPITAL CHARACTERISTICS. The NHC data were linked with the American Medical Association Physician Masterfile (27,28) using the unique physician identification number of the attending physician, who was defined as the clinician primarily responsible for the patient's care during hospitalization (29). Hospital characteristics were ascertained by linking with American Hospital Association Annual Surveys (30,31). Dates of death were identified with the Medicare Enrollment Database (32).

Readmission data were ascertained using Medicare Part A administrative files.

OUTCOME VARIABLES. To identify correlates of aspirin prescription, we designated the outcome of interest as the documentation of aspirin in the medication regimen at hospital discharge, in either prescription or nonprescription forms. For outcomes analyses, the primary outcome was death at one year. Secondary outcomes included the composite of death or readmission for all causes and the composite of death or readmission for heart failure. Follow-up of at least one year was available for all patients.

Statistical analysis. Bivariate comparisons between patients treated and not treated with aspirin were performed with chi-square tests for categorical variables and the Wilcoxon rank sum test for continuous variables. Rates of aspirin prescription by state were calculated. All analyses were performed with probability weights, based upon the inverse sampling fraction for each state, to obtain estimates that are representative of the total number of heart failure admissions nationwide during the sampling period.

To identify the patient and provider characteristics associated with aspirin, we constructed multivariable hierarchical logistic models accounting for the clustering of patients by hospital (33). Variables with a univariate $p < 0.05$ or variables considered clinically important were candidates for the model. Final parameters were estimated in a hierarchical model with probability weights and a random intercept for hospital.

To assess the relationship between aspirin and outcomes, we used hierarchical logistic regression models with the event within one year as the dependent variable. In addition to a variable for aspirin treatment, patient level variables (demographics, cardiac comorbidities, noncardiac comorbidities, left ventricular [LV] function, discharge treatment with ACE inhibitors, and discharge treatment with beta-blockers), hospital characteristics, and physician characteristics were tested. All statistically or clinically significant variables were retained in the final model. To assess for heterogeneity in the effect of aspirin in clinically important patient strata, we determined the significance of the interaction among aspirin prescription and age, gender, the presence or absence of hypertension, LV systolic dysfunction, estimated GFR, and the discharge prescription of ACE inhibitors and beta-blockers individually with the inclusion of a cross-product term of aspirin treatment with the stratification variables. To test for differences in the relationship between ACE inhibitor prescription and mortality according to aspirin treatment, we constructed stratified models assessing the odds ratio for discharge prescription of ACE inhibitors stratified by aspirin use.

Unadjusted rates and performed exploratory and descriptive analyses were performed with the SAS version 8.2 statistical software (SAS Institute, Cary, North Carolina). The STATA version 7.0 (STATA Corp., College Station, Texas) was used for the mortality model to account for the sample design and probability weights. Final model parameters for the hierarchical model with probability weights for aspirin prescription were estimated in MLwiN version 1.1 (Centre for Multilevel Modelling, Institute of Education, University of London, London, United Kingdom). All odds ratios were converted to estimated risk ratios (RRs) (34).

RESULTS

Patient characteristics. Of the NHC cohort, 24,012 patients satisfied the inclusion criteria for this study. The mean age of the study cohort was 79 ± 8 years. Among all patients in the study cohort, 13,049 (54%) were discharged on aspirin. Patients receiving aspirin were younger, and greater proportions were white and male compared with those not treated (Table 1). Compared to patients not treated with aspirin, a greater proportion of patients treated had a history of myocardial infarction (MI) and/or coronary revascularization; a higher prevalence of coexisting cardiovascular conditions, including hypertension and cerebrovascular disease; and higher rates of treatment at discharge with ACE inhibitors and beta-blockers. A lower prevalence of noncardiovascular comorbidity (e.g., obstructive lung disease or dementia) was present in patients treated with aspirin.

Patterns of treatment. Marked variation in aspirin prescription existed by state, with rates ranging from 31% to 70%. Patients with more severe CAD received aspirin more frequently as part of their discharge regimen: of those without previous MI or revascularization, 45% were treated, whereas those with previous MI, revascularization, or both were treated more frequently (54%, 55%, and 61%, respectively, p for trend <0.001) (Fig. 1). However, the variation in rates treatment by state across strata of CAD severity remained marked.

In the multivariable analysis, MI, revascularization, or both and symptoms of angina were associated with higher likelihood of aspirin treatment (Table 2). Patients with hypertension were slightly more likely to receive aspirin (RR 1.03; 95% confidence interval [CI] 1.00 to 1.06), but those with a lower estimated GFR were equally likely as those with higher estimated GFR to receive aspirin. Among provider characteristics, discharge from teaching hospitals and care by a cardiologist were associated with a greater likelihood of aspirin treatment. Processes of care, including discharge prescriptions for ACE inhibitors and beta-blockers, were also associated with a higher likelihood of aspirin treatment. Patients receiving care from cardiologist attending physicians and in teaching hospitals were more likely to receive aspirin, whereas those receiving care in for-profit hospitals had a lower adjusted likelihood of being treated.

Treatment and outcomes. Patients treated with aspirin had significantly lower crude mortality rates compared with those not treated (31% vs. 39%, $p < 0.001$). Although rates of readmission for all causes (78% vs. 78%, respectively, $p = 0.8$) or for heart failure (69% vs. 70%, $p = 0.4$) were similar

Table 1. The Patient Population

	Total (n = 24,012)	Not Treated With Aspirin (n = 10,963)	Treated With Aspirin (n = 13,049)	p Value*
Demographics				
Age, mean (±SE)	79.4 ± 0.067	79.8 ± 0.098	78.9 ± 0.012	<0.001
Age categories, yrs				<0.001
65–74	29%	27%	31%	
75–84	43%	44%	43%	
85+	28%	29%	26%	
Gender, female	58%	60%	56%	<0.001
Race				<0.001
Caucasian	84%	83%	84%	
African American	12%	11%	12%	
Other nonwhite	5%	5%	5%	
Admitted from SNF	9%	12%	7%	<0.001
Coronary history				<0.001
CAD without previous MI or revascularization	34%	40%	29%	
Previous MI	27%	26%	28%	
Previous revascularization	19%	18%	20%	
Previous MI and revascularization	20%	16%	23%	
Other medical history				
Angina pectoris	26%	23%	29%	<0.001
Hypertension	68%	66%	70%	<0.001
Atrial fibrillation	20%	22%	18%	<0.001
Stroke	17%	17%	17%	0.99
Chronic lung disease	36%	39%	34%	<0.001
Diabetes mellitus	44%	41%	42%	0.49
Dementia	9%	10%	8%	0.001
Estimated GFR (ml/min/1.73 m^2)				0.40
>59	31%	32%	31%	
30–59	53%	53%	54%	
<30	15%	15%	15%	
LV systolic function				<0.001
Preserved	32%	31%	34%	
Impaired	36%	32%	39%	
Not documented	32%	37%	28%	
Discharge medications				
ACE inhibitors	53%	46%	60%	<0.001
Beta-blockers	31%	23%	38%	<0.001
Diuretics	85%	79%	91%	<0.001
Provider characteristics				
Teaching hospital	37%	34%	40%	<0.001
For-profit hospital	13%	15%	11%	<0.001
Cardiologist	23%	20%	26%	<0.001

*p values comparing patients not treated with aspirin and those treated with aspirin.
ACE = angiotensin-converting enzyme; CAD = coronary artery disease; GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction; SNF = skilled nursing facility.

between the two groups, patients treated with aspirin had lower rates of the composite of death and all cause-readmission (85% vs. 89%, $p < 0.001$) and death and readmission for heart failure (79% vs. 83%, $p < 0.001$) than those who were not treated.

After adjustment for age, gender, and clinical risk factors, aspirin prescription was associated with significantly lower risks of death (RR 0.94; 95% CI 0.89 to 0.99) (Table 3). This association did not differ significantly in strata of patient age, gender, or the presence of hypertension, elevated serum creatinine, LV systolic dysfunction, or ACE inhibitor prescription (Table 3, p value for all interactions ≥0.5). Conversely, the association between ACE inhibitor prescription and mortality (in all patients RR 0.92; 95% CI 0.87 to 0.96) did not differ between patients treated with aspirin (RR 0.92; 95% CI 0.85 to 0.99) and those not treated (RR 0.91; 95% CI 0.85 to 0.98; p value for interaction = 0.8).

In multivariable analyses of the secondary composite end points, the discharge prescription of aspirin was associated with lower risks of death or readmission for all causes (RR 0.98; 95% CI 0.97 to 0.99) and for death or readmission for heart failure (RR 0.98; 95% CI 0.96 to 0.99).

DISCUSSION

In this national cohort of patients hospitalized with heart failure and CAD, 48% did not receive aspirin at hospital

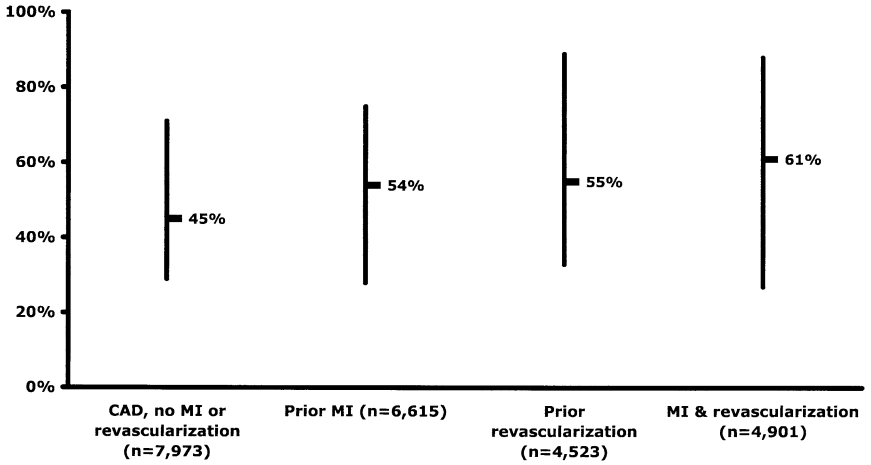

Figure 1. Weighted median national rates and ranges of state rates of aspirin prescription for Medicare beneficiaries with heart failure as a function of coronary artery disease (CAD) severity in the U.S., 1998 to 2001 (p value for trend across categories of CAD severity <0.001). MI = myocardial infarction.

discharge, and treatment rates varied markedly by state. Although rates of prescription were higher in those with previous MI, revascularization, or angina, >40% of patients with these important sequelae of CAD were not treated.

Table 2. Factors Associated with Aspirin Prescription at Hospital Discharge

	RR (95% CI)
Demographics	
Age, yrs	
65–74	1.00 (ref.)
75–84	0.99 (0.96–1.01)
≥85	0.96 (0.93–1.00)
Female gender	0.96 (0.94–0.99)
Nonwhite race	0.98 (0.94–1.02)
Coronary history*	
CAD without previous MI or revascularization	1.00 (ref.)
Previous MI	1.15 (1.11–1.19)
Previous revascularization	1.18 (1.13–1.22)
Previous MI and revascularization	1.29 (1.24–1.33)
Other medical history	
Angina pectoris*	1.15 (1.12–1.18)
Hypertension*	1.03 (1.00–1.06)
Atrial fibrillation*	1.04 (1.01–1.06)
Stroke	1.00 (0.97–1.04)
Diabetes mellitus	0.97 (0.95–1.00)
GFR (ml/min/1.73 m^2)	
>59	1.00 (ref.)
30–59	1.03 (1.00–1.06)
<30	1.00 (0.96–1.04)
LV systolic function*	
Preserved	1.00 (ref.)
Impaired	1.02 (0.99–1.05)
Not documented	0.88 (0.85–0.91)
Discharge medications	
ACE inhibitor*	1.27 (1.24–1.30)
Beta-blocker*	1.32 (1.29–1.35)
Provider characteristics	
Teaching hospital*	1.06 (1.03–1.10)
For-profit hospital*	0.88 (0.83–0.93)
Cardiologist attending*	1.16 (1.12–1.19)

*Statistically significant correlation in the multivariable model ($p < 0.05$).
CAD = coronary artery disease; ref. = referent group; RR = risk ratio; other abbreviations as in Table 1.

Aspirin treatment was associated with a reduction in the risk of death that was consistent regardless of the presence or absence of hypertension, elevated serum creatinine, or co-prescription of ACE inhibitors. Furthermore, aspirin did not attenuate the benefit of ACE inhibitors. These results suggest that current patterns of practice may deprive many patients with both CAD and heart failure from important benefits from the use of an inexpensive drug.

The patterns of use observed in this study provide possible explanations for the factors motivating treatment with aspirin. Although patients with previous serious coro-

Table 3. Risk Ratios for One-Year Mortality Associated With Aspirin Treatment in Subgroups

	Adjusted RR (95% CI)*
All patients	0.94 (0.89–0.99)
Age group, yrs	
65–74	0.96 (0.85–1.07)
74–84	0.91 (0.85–0.99)
≥85	0.94 (0.86–1.01)
Gender	
Male	0.95 (0.87–1.02)
Female	0.93 (0.86–1.00)
Hypertension	
No	0.89 (0.81–0.96)
Yes	0.97 (0.90–1.03)
Estimated GFR (ml/min/1.73 m^2)	
>59	0.99 (0.89–1.09)
30–59	0.92 (0.85–0.99)
<30	0.91 (0.81–1.00)
Left ventricular systolic function	
Preserved	1.01 (0.88–1.15)
Impaired	0.92 (0.84–1.00)
Not documented	0.96 (0.88–1.03)
ACE inhibitor treatment	
No	0.93 (0.87–1.00)
Yes	0.94 (0.87–1.01)
Beta-blocker	
No	0.95 (0.89–1.01)
Yes	0.87 (0.78–0.99)

*$p > 0.05$ for interaction between aspirin prescription and all subgroups.
Abbreviations as in Tables 1 and 2.

nary events and those with symptomatic CAD were more likely to receive aspirin, overall rates of use were low compared with other studies of populations with the primary diagnosis of CAD, perhaps in part because many of the patient's presentations were dominated by heart failure (19,20,22,23). Aspirin prescription was positively correlated with ACE-inhibitor treatment, implying that concerns about drug interactions did not entirely explain treatment decisions. Additionally, both the prescription of beta blockers and the documentation of LV function—guideline-recommended processes of care for patients with CAD and heart failure, respectively (4,24)—were associated with higher rates of aspirin prescription.

Although aspirin is an inexpensive and effective treatment in reducing death and events in a broad range of patients with CAD, its use in patients with heart failure has been the center of controversy (35–38). Aspirin and other nonsteroidal anti-inflammatory agents may antagonize the vasodilator effects of ACE inhibitors (5), exacerbate hypertension, decrease GFR (6,7), and attenuate the effects of diuretics (8), all of which could be particularly detrimental in patients with heart failure. Furthermore, by causing renal insufficiency, aspirin may limit the possibility of achieving optimal doses of ACE inhibitors in some patients. In this study, however, no evidence was found that hypertension or renal insufficiency contributed significantly to the decision to prescribe aspirin in patients with heart failure.

Among patients with heart failure, CAD is common (25,39), and vascular events are a common cause of death in patients with CAD and concomitant heart failure (40). Despite the preponderance of CAD, the use of aspirin in patients with heart failure has not been clarified by the existing evidence. Post-hoc subgroup analyses of randomized clinical trials, many of which assess patients after acute MI, have provided mixed results (9–14). Observational studies of cohorts with heart failure with CAD have also produced conflicting data in relatively small samples of patients (15–18). This investigation, which is the largest observational study of the topic to date in a nationally representative cohort of patients with heart failure in the context of contemporary patterns of treatment, suggests no evidence of harm from aspirin use and the possibility of important benefits in this patient population.

The relative risk reduction for mortality associated with aspirin prescription in this study (6% with confidence intervals ranging from 1% to 10%) is lower than that reported by other studies of aspirin as secondary prevention in other high-risk populations such as those after acute MI, unstable angina, or stroke (41–44). Because the primary benefit of aspirin is likely by the reduction of vascular events, the risk reduction in death from vascular causes in patients with multiple types of comorbidity may be diluted by competing mortality from heart failure and noncardiovascular causes. Because we were not able to ascertain the causes of death in this cohort, we could not determine the effects of aspirin on vascular death. Nevertheless, even a smaller risk reduction could have important implications for high-risk patients.

Current guidelines, although acknowledging the theoretical possibility of an antagonistic interaction between aspirin and ACE inhibitors, classify antiplatelet treatment in patients with heart failure and concomitant CAD a level IIa recommendation (a condition for which there is conflicting evidence about efficacy but where the weight of evidence is in favor of efficacy) (24). The uncertainty surrounding the benefit of aspirin in patients with heart failure and the lack of a class I recommendation may explain some of the marked variation in prescription patterns described in this study. Our data support the use of aspirin in patients with heart failure and CAD, including those treated with ACE inhibitors.

Study limitations. Several issues merit consideration in the interpretation of these results. Because this study was observational, it remains possible that unmeasured variation among patients could confound the results. However, we adjusted for a wide range of differences in patients, providers, and other medical therapy in our analysis and accounted for the clustering of patients at the hospital level. Additionally, we restricted the cohort to patients without contraindications to aspirin prescription, reducing the likelihood of confounding by indication. Our study suggests aspirin has clinically important benefit in this population and no indication of harm. Although randomized trials are the ideal means of assessing this question, placebo-controlled trials of adequate size studying aspirin in patients with CAD and heart failure are unlikely because of concerns of withholding aspirin from such patients.

We were not able to assess the use of aspirin during the follow-up period. Thus, some of the patients treated with aspirin or ACE inhibitors at discharge may not have been treated during follow-up and, conversely, these medications might have been initiated later in those initially not treated. Classifying patients based on the discharge medications would have biased our results to the null. Because dosing information was not available, we were not able to assess the relationship between aspirin doses and outcomes in this study. This study population includes only older fee-for-service Medicare beneficiaries hospitalized primarily for heart failure. Thus, although it may not be appropriate to generalize the findings of this study to the entire elderly U.S. population with heart failure, we have examined a nationally representative and important subset of this population that suffers a substantial burden of morbidity and mortality. Furthermore, this cohort is likely more representative of the population with heart failure than randomized trials populations with respect to age, gender, racial, and comorbidity profile.

Conclusions. The prescription of aspirin to patients with heart failure and CAD varies markedly in the U.S., and nearly half such patients are not treated after discharge for hospitalization for heart failure. Aspirin treatment was not associated with an increased risk of mortality or readmission but was associated with lower risk of adverse outcomes, even in patients with hypertension or renal dysfunction, and those treated with ACE inhibitors. Furthermore, there was no evidence that aspirin attenuates the benefits of ACE inhibitors. Withholding this inexpensive treatment may deprive patients with CAD and concomitant heart failure of important clinical benefits.

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APPENDIX

For the candidate variables for the adjusted models, please see the online version of this article.