Effects of Angiotensin-Converting Enzyme Inhibitors and Digoxin on Health Outcomes of Very Old Patients With Heart Failure

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Background: Randomized trials have shown that angiotensin-converting enzyme (ACE) inhibitors reduce mortality and morbidity, and improve symptoms and exercise tolerance in selected patients with congestive heart failure (CHF). There is, however, no evidence on the effectiveness of ACE inhibitors in the typical, very old and frail patients with CHF.

Objective: To compare the effects of ACE inhibitors and digoxin on 1-year mortality, morbidity, and physical function among patients aged 85 years.

Methods: We conducted a retrospective cohort study using the SAGE database, a long-term care database linking patient information with drug utilization data. Among 64,637 patients with CHF admitted to all nursing homes in 5 states between 1992 and 1995, we identified 19,492 patients taking either an ACE inhibitor (n = 4,911) or digoxin (n = 14,890). Record of date of death was derived from Medicare enrollment files, and we used the part A Medicare files to identify hospital admissions and discharge diagnoses. As a measure of physical function, we used a scale for activities of daily living performance. The effect of ACE inhibitors was estimated using Cox proportional hazards models with digoxin users as the reference group.

Results: The overall mortality rate among ACE inhibitor recipients was more than 10% less than that of digoxin users (relative rate, 0.89; 95% confidence interval, 0.83-0.95). Morbidity was equally reduced regardless of concomitant cardiovascular conditions and baseline physical function. Treatment with ACE inhibitors was associated with a tendency toward reduced hospital admissions that was more evident among patients with greater functional impairment. The adjusted relative rate for hospitalization for any reason was 0.96 (95% confidence interval, 0.91-1.01). The rate of functional decline was greatly reduced among ACE inhibitor recipients (relative rate, 0.74; 95% confidence interval, 0.69-0.80), and this effect was consistent and independent of background comorbidity and baseline physical function.

Conclusions: These data suggest that survival and functional benefits of ACE inhibitor therapy extend to patients with CHF 85 years and older, and mostly women, both systematically underrepresented in randomized trials. Alternatively, digoxin has a detrimental effect in this population.

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PATIENTS AND METHODS

We used data from the Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) database. This population-based data set combines (1) patient information collected with the Minimum Data Set (MDS), (2) data on any medication used by each nursing home resident, (3) death and health service use documentation via linkage to Medicare files, and (4) facilities' characteristics as collected in the On-line Survey Certification Automated archive. The SAGE database has been described in detail elsewhere, and it is briefly summarized herein.

THE SAGE DATABASE

The MDS data were collected as part of the Health Care and Financing Administration’s Multi-State, Case-Mix and Quality Demonstration Project that assessed all residents in all Medicare/Medicaid-certified nursing homes (n = 1492) of 5 states (Kansas, Maine, Mississippi, New York, and South Dakota) from 1992 to 1995. The MDS is a 350+ item instrument used to assess all residents in the long-term care facilities across the United States. The MDS provides reliable scoring of comprehensive clinical parameters, including an extensive array of diagnoses, signs, symptoms, syndromes, and treatments, along with functional status, cognition, and behavior.

The MDS data were linked to a drug utilization file listing all drugs consumed by each resident during the 7 days preceding the assessment. Up to 18 different drugs were coded according to the National Drug Codes, and information included brand and generic name, dose, route and frequency of administration, and whether standing prescription or as needed (prn; pro re nata). The National Drug Codes were then matched (≥95%) to the Master Drug Data Base (MediSpan Inc, Indianapolis, Indiana), containing complete records for prescription drug products in the retail pharmacy environment. The MDS and pharmacological data were also linked to the Medicare enrollment files (HISKEW; Health Insurance Skeletonized Write-off file). Overall, nearly 85% of residents matched to HISKEW files. We then cross-linked residents with MDS data to the Medicare inpatient claims database (part A) containing information on all health services for which a claim had been filed between 1991 and 1997.

We have previously documented that many data elements of the SAGE database have excellent validity, and the database has proved a useful and reliable tool for pharmacoepidemiological research.36-38

STUDY POPULATION

Among 351,224 unique nursing home residents (1992-1995), we identified 64,637 patients with a diagnosis of CHF who were admitted to the facility upon discharge from an acute care hospital. Our cohort was then restricted to patients who at first assessment were receiving a mutually exclusive treatment with either digoxin (MediSpan class 31.20) or an ACE inhibitor (MediSpan class 36.10). Of the 27,854 patients identified, we excluded the following: (1) patients younger than 65 years (n = 870); (2) those without a valid match to Medicare enrollment files (n = 5047); (3) patients admitted to a nursing home upon discharge from the hospital and rehospitalized within 30 days (n = 800); (4) those in a comatose state (n = 57); and (5) patients who died within 30 days of nursing home admission (n = 1279). Our study population consisted of 19,492 remaining patients, 14,890 receiving digoxin and 4911 patients receiving an ACE inhibitor.

ANALYTIC DESIGN

Outcome Information

We evaluated the effect of ACE inhibitors on the rate of (1) overall mortality, (2) hospitalization, and (3) mortalization, and improve symptoms and exercise tolerance. In contrast, despite being a cornerstone of CHF therapy for more than a century, digoxin’s role is now controversial. Some trials have suggested that worsening heart failure and hospitalization occurred less often in patients treated with digoxin.21 However, a recent placebo-controlled study has demonstrated digoxin’s inability to substantially influence morbidity and mortality.22 This is reflected in the recommendation that digitalis be used only in patients who remain symptomatic after optimal management with ACE inhibitors.23,24

Nonetheless, these trials have almost invariably excluded elderly patients,25,26 especially the oldest ones, and greatly underrepresented women.27 Moreover, these trials have screened out patients with preserved systolic function,28 thereby limiting the generalizability of the findings. Thus, despite the epidemiological relevance of CHF among older individuals, there is a paucity of data to elucidate optimal management strategies of the more typical patients with CHF.29,30 In fact, old age and female sex are both independent predictors of CHF associated with preserved systolic function,31 a condition that may affect as many as 74% of older CHF patients.28,31

To address some of these issues, we conducted a retrospective cohort study comparing the effects of therapy with an ACE inhibitor or with digoxin on all-cause mortality, hospitalization, and physical function in very old patients (mean age, 85 years) with heart failure.

PATIENT CHARACTERISTICS

The sociodemographic characteristics of patients and several indicators of functional status, disease severity, and comorbidity by baseline pharmacological therapy are illustrated in Table 1. Digoxin users were slightly older than patients receiving an ACE inhibitor (85.4 vs 83.9 years); no major sex or race differences were evident. Digoxin users were more likely to have a greater degree of physical function impairment and to be underweight than patients receiving an ACE inhibitor. The prevalence of selected, disease-specific physical signs (eg, edema and dyspnea) did not differ in the 2 groups. Among the concurrent cardiovascular diagnoses, ischemic heart disease was slightly more prevalent among recipients of di-
physical function decline. We considered disease of the circulatory system as a whole (International Classification of Diseases, Ninth Revision [ICD-9]) codes 390-459) or as follows: hypertensive disease (401-405), ischemic heart disease (410-414), atrioventricular blocks (426.0, 426.1, 426.6, 426.9), atrial fibrillation and flutter (427.3), ventricular fibrillation/cardiac arrest (427.4, 427.5), paroxysmal tachycardia (427.0-427.2), other arrhythmias (427.6, 427.8), worsening CHF (428.0-428.9), and cerebrovascular disease (430.0-436).

To ascertain physical functioning, we used a 5-item, 6-level activities of daily living (ADL) scale. We defined as decline in physical functioning any increase in the ADL score from the previous assessment, over a 1-year period. As the incident date to calculate the person-years of follow-up, we used the date of death from the Medicare enrollment file for mortality analyses, the date of the earliest inpatient admission from the Medicare inpatient files for each hospitalization outcome, and the date of first decline in ADL performance.

Potential Confounders

Sociodemographic variables, indicators of physical functioning and disease severity, and comorbid conditions were considered as potential confounders. Functional indicators included baseline ADL score, signs and symptoms of CHF (ie, edema, shortness of breath), and a body mass index of 19 kg/m² or less. Severity indicators considered were secondary cardiovascular diagnoses, such as ischemic heart disease and hypertension, and concomitant drug use. Furthermore, as another measure of disease severity, we determined the total and all cardiovascular-related hospital admissions within the year prior to initial MDS assessment. We also identified recipients of digoxin (40% vs 34% in ACE inhibitor users), while hypertension was almost double in the group of patients treated with an ACE inhibitor (52% vs 29% in digoxin users). Arrhythmias were more prevalent among recipients of digoxin relative to ACE inhibitor users (27% vs 14% in ACE inhibitor users). A greater percentage of patients receiving an ACE inhibitor had diabetes mellitus (27% vs 22% in digoxin users). There were no differences in the number of drugs taken in addition to digoxin or ACE inhibitors, nor in the use of specific cardiovascular medications except for nitrates. Nearly half of the patients in both groups were receiving a diuretic, furosemide in more than 95% of cases. History of hospitalizations, for both cardiac and noncardiac reasons, in the year prior to the first assessment was similar in both groups.

EFFECT OF ACE INHIBITORS ON MORTALITY, HOSPITAL ADMISSION, AND PHYSICAL FUNCTION

Table 2 shows that, after adjusting for all the variables listed in Table 1, the rate of all-cause mortality among ACE inhibitor recipients was 10% less than that for recipients of digoxin (relative rate [RR], 0.89; 95% CI, 0.83-0.95). The rate of new hospital admission for any cause among ACE inhibitor users was about 5% less than that of patients treated with digoxin, although the CIs included unity (RR, 0.96; 95% CI, 0.91-1.01). The rate of death or hospitalization for any cause was similarly reduced (RR, 0.95; 95% CI, 0.92-1.00). Patients receiving an ACE inhibitor tended to have been hospitalized less quickly as a result of worsening heart failure (RR, 0.96; 95% CI, 0.89-1.03), bradyarrhythmia (RR, 0.91; 95% CI, 0.70-1.18), ischemic heart disease (RR, 0.93; 95% CI, 0.84-1.00), and stroke (RR, 0.92; 95% CI, 0.76-1.11). On the other hand, patients receiving an ACE inhibitor were hospitalized at a faster rate for acute renal failure relative to patients receiving digoxin (RR, 1.40; 95% CI, 1.05-1.89). Strikingly, among patients receiving an ACE inhibitor, the rate of functional decline was approximately 25% lower than that of patients receiving digoxin therapy (RR, 0.74; 95% CI, 0.69-0.80). When we restricted the analysis to patients who survived at least 90 days after initial MDS assessment (n = 13 270), the rate of functional decline was still significantly attenuated by treatment with an ACE inhibitor (RR, 0.86; 95% CI, 0.79-0.94).

STATISTICAL ANALYSIS

The effect of ACE inhibitors was estimated using Cox proportional hazards models, with digoxin users as the reference group, and simultaneously controlling for all the potential confounding variables. We utilized ACE inhibitor use within the year of follow-up as a time-varying independent variable. To maintain the reference group as those receiving digoxin therapy, we included a term for the initiation of combination therapy as a time-varying covariate. Because the goal of our analysis was to provide an estimate of the effect of ACE inhibitors on the outcomes of interest adjusted for potential confounders, we did not use statistical significance to guide our decisions about which variables would remain in the models. To evaluate whether the effect of ACE inhibitors on mortality and hospitalization differed by baseline physical function, we performed a stratified analysis by baseline ADL score. We categorized impairment in physical function as mild (ADL score, 0-1), moderate (ADL score, 2-3), or severe (ADL score, 4-5). For the hospitalization outcomes, we censored residents at their time of death to adjust for the competing risk. Similarly, for the analysis of decline in physical function, we censored residents at their time of death, time of first hospitalization, or at their initial assessment if they were completely dependent (ADL score of 5). We also performed an additional analysis restricted to patients who survived at least 90 days after the initial MDS assessment. We examined the log-log survival function to evaluate (and rule out) departures from the proportionality assumption for each model. From these models, we derived estimates of effect and corresponding 95% confidence intervals (CIs). We performed all analyses using SAS software (version 6.12; SAS Institute, Cary, NC).
similar, with a tendency toward increased advantage (RR, 0.82; 95% CI, 0.74-0.90). The adjusted RR for hospitalization magnitude among patients with hypertension (RR, 0.82; 95% CI, 0.74-0.90). The adjusted RR for hospitalization among patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; 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the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) significant cardiovascular condition; the estimates were similar in patients with (RR, 0.90) and without (RR, 0.89) The rate of decline in physical function was substantially reduced by treatment with an ACE inhibitor, and this effect was independent of background comorbidity. The estimates of the RR were similar in all groups, ranging between 0.68 (95% CI, 0.56-0.84) for patients with arrhythmia and 0.77 (95% CI, 0.69-0.85) for patients without hypertension.

### IMPACT OF BASELINE PHYSICAL FUNCTION ON EFFECT OF ACE INHIBITORS

In Table 4, the effect of ACE inhibitors relative to digoxin use was analyzed stratifying patients by baseline physical function. After controlling for all measured confounders, we observed similar effects on the mortality rate across all ADL strata. The adjusted RR for death was 0.88 (95% CI, 0.80-0.98) for patients with severe impairment in physical function, compared with 0.89 (95% CI, 0.73-1.09) and 0.92 (95% CI, 0.84-1.00) among patients with only mild or moderate impairment, respectively. Among patients with severe impairment, the adjusted RR of hospitalization for any cause was 0.94 (95% CI, 0.86-1.03) and that for any cardiovascular reason was 0.97 (95% CI, 0.88-1.07). A comparatively similar effect was observed among patients with moderate impairment, but not among those with mild forms of CHF. On the other hand, the benefit provided by ACE inhibitor use on the rate of physical function decline was independent of baseline ADL level and ranged between 25% and 30%.

### COMMENT

In a cohort of very old CHF patients living in long-term care facilities, we found that treatment with an ACE inhibitor compared with digoxin was associated with a prolonged 1-year survival, and with a substantially reduced rate of functional decline. Mortality and functional decline were equally reduced regardless of concomitant cardiovascular conditions and of baseline physical func-
Table 3. Effects of ACE Inhibitors on All Outcomes by Presence or Absence of Hypertension and Arrhythmia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Hypertension</th>
<th>Hypertension</th>
<th>No Arrhythmia</th>
<th>Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events,</td>
<td>No. of Events,</td>
<td>No. of Events,</td>
<td>No. of Events,</td>
</tr>
<tr>
<td></td>
<td>ACE Inhibitor (n = 10 620)/Digoxin (n = 2352)</td>
<td>ACE Inhibitor (n = 4270)/Digoxin (n = 2559)</td>
<td>ACE Inhibitor (n = 10 857)/Digoxin (n = 4231)</td>
<td>ACE Inhibitor (n = 4033)/Digoxin (n = 688)</td>
</tr>
<tr>
<td>Relative Rate (95% CI)†</td>
<td>Relative Rate (95% CI)†</td>
<td>Relative Rate (95% CI)†</td>
<td>Relative Rate (95% CI)†</td>
<td>Relative Rate (95% CI)†</td>
</tr>
<tr>
<td>Death</td>
<td>3513/793</td>
<td>3132/711</td>
<td>3512/793</td>
<td>1333/211</td>
</tr>
<tr>
<td></td>
<td>0.95 (0.87-1.04)</td>
<td>0.82 (0.74-0.90)</td>
<td>0.89 (0.83-0.96)</td>
<td>0.90 (0.76-1.05)</td>
</tr>
<tr>
<td>CV hospitalization‡</td>
<td>3936/931</td>
<td>1763/1042</td>
<td>4901/1671</td>
<td>1727/319</td>
</tr>
<tr>
<td></td>
<td>1.00 (0.93-1.09)</td>
<td>0.95 (0.88-1.03)</td>
<td>0.97 (0.91-1.02)</td>
<td>0.97 (0.86-1.11)</td>
</tr>
<tr>
<td>Any hospitalization‡</td>
<td>4406/1922</td>
<td>1089/1124</td>
<td>4631/1813</td>
<td>2303/296</td>
</tr>
<tr>
<td></td>
<td>1.00 (0.93-1.09)</td>
<td>0.95 (0.88-1.03)</td>
<td>0.97 (0.91-1.02)</td>
<td>0.96 (0.85-1.08)</td>
</tr>
<tr>
<td>Death or hospitalization</td>
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<td>2420/1373</td>
<td>5992/2329</td>
<td>1083/160</td>
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<td></td>
<td>1.00 (0.94-1.07)</td>
<td>0.94 (0.87-1.02)</td>
<td>0.97 (0.92-1.01)</td>
<td>0.68 (0.56-0.84)</td>
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<td>Decline in physical function§</td>
<td>2875/593</td>
<td>1110/615</td>
<td>2902/1048</td>
<td>2030/396</td>
</tr>
<tr>
<td></td>
<td>0.77 (0.69-0.85)</td>
<td>0.71 (0.63-0.80)</td>
<td>0.75 (0.69-0.82)</td>
<td>0.96 (0.85-1.08)</td>
</tr>
</tbody>
</table>

*Explanations of the footnote symbols are the same as those given in Table 2.

Table 4. Effect of ACE Inhibitors and Digoxin on Outcomes of Patients Stratified According to Baseline Functional Impairment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td></td>
<td>Relative Rate (95% CI)†</td>
<td>Relative Rate (95% CI)†</td>
<td>Relative Rate (95% CI)†</td>
</tr>
<tr>
<td>Death</td>
<td>0.89 (0.73-1.09)</td>
<td>0.92 (0.84-1.00)</td>
<td>0.88 (0.80-0.98)</td>
</tr>
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<td>CV hospitalization‡</td>
<td>1.07 (0.93-1.23)</td>
<td>0.97 (0.89-1.05)</td>
<td>0.97 (0.88-1.07)</td>
</tr>
<tr>
<td>Any hospitalization‡</td>
<td>1.08 (0.94-1.24)</td>
<td>0.95 (0.88-1.03)</td>
<td>0.94 (0.86-1.03)</td>
</tr>
<tr>
<td>Death or hospitalization</td>
<td>1.03 (0.91-1.17)</td>
<td>0.97 (0.91-1.04)</td>
<td>0.96 (0.87-1.02)</td>
</tr>
<tr>
<td>Decline in physical function§</td>
<td>0.76 (0.65-0.88)</td>
<td>0.73 (0.66-0.81)</td>
<td>0.71 (0.59-0.86)</td>
</tr>
</tbody>
</table>

*Explanations of the footnote symbols are the same as those given in Table 2. Functional impairment was assessed as follows: mild: a 0-1 score on activities of daily living (ADL) scale (digoxin, n = 2117, ACE inhibitor, n = 748); moderate: a 2-3 score on ADL scale (digoxin, n = 6705, ACE inhibitor, n = 2435); and severe: a 4-5 score on ADL scale (digoxin, n = 5989, ACE inhibitor, n = 1707).

EFFECT ON MORTALITY

Several studies have reported improved survival when CHF patients with systolic dysfunction are treated with ACE inhibitors.18-20,41 Although the survival benefit has been demonstrated across an age spectrum, our study is the first to indicate that survival benefit extends to include very old patients (mean age, 85 years). The estimates of effect are consistent with the results of 39 randomized trials summarized by Garg and Yusuf,19 and by the North of England ACE Inhibitor Guideline Development Group.20 Overall, these trials indicated a 17% reduction in mortality with a pooled RR of 0.83 (95% CI, 0.76-0.90). We found an 11% reduction, but this slightly smaller survival benefit must be considered in light of a longer follow-up and the poor prognosis of this population.42,43

In the SOLVD trial, the size of the survival benefit conferred by ACE inhibitor therapy correlated with left ventricular systolic dysfunction: the lower the ejection fraction the greater the benefit.44,45 Similarly, a distinction of all the trials based on a normalized annual mortality of up to or more than 15% evidenced a greater survival benefit among patients in the high-risk group.20 In the present study we found that mortality was equally reduced regardless of baseline physical function, as measured by ADL performance. While these data could appear in contrast with previous results, a direct comparison is not warranted since the great majority of patients in the trials were New York Heart Association (NYHA) class II to III (ie, moderate ADL impairment).

EFFECT ON HOSPITALIZATION

Randomized trials consistently showed a reduction in hospital admissions for progressive CHF in patients taking ACE inhibitors.18-20,41 In the present study we observed only a tendency toward an overall lower rate of hospitalization. Yet, given the frailty of our population and the high rate of hospital admissions,46 any benefit of ACE inhibitor use would be difficult to detect. If any, the effect of ACE inhibitors on the rate of hospitalization appeared restricted to patients with a moderate to severe ADL impairment. This observation may appear not immediately reconcilable with trials that found the combined end point of total mortality or hospitalization consistently reduced regardless of baseline functional status as measured by NYHA class.19 However, it should be noted that very few patients with NYHA class I (ie, mild ADL impaired) were randomized in trials, and that those were specifically the patients with this level of impairment for whom we observed a trend toward an increased rate of hospitalization. It is possible that in the face of a somewhat lower intrinsic rate, variations in practice and policy across facilities become important determinants of hospitalization.47 For example, there is evidence that approximately 50% of CHF hospitalizations are low risk and possibly avoidable.48
EFFECT ON PHYSICAL FUNCTION

We found that the rate of functional decline among ACE inhibitor users was 25% to 30% less than that of digoxin users, with little influence of the baseline level. This is in agreement with the findings of Narang et al., who reviewed 35 double-blind, placebo-controlled trials including altogether 3411 patients with symptomatic CHF. An improvement in exercise tolerance and patients’ symptoms was documented in more than two thirds of the studies.

In the above-mentioned trials, exercise tests, particularly measurements of exercise time or distance, peak workload, and maximal oxygen consumption, were the standard parameters for the evaluation of physical function. However, the exercise tolerance test may not be a feasible way to assess physical functioning of older and frail patients. In our study, we used a comprehensive assessment of ADL performance, a measure that has proved to be a more powerful predictor of death than conventional clinical measures in these patients. In fact, while formal laboratory-based measurements are more likely to reflect cardiovascular fitness, daily activity levels correlate with the skeletal muscle abnormalities that generate CHF symptoms but bear no relation to the degree of central hemodynamics. Moreover, ADL scores may encompass psychological or other factors, in addition to physical capability, which might have independent effects on survival.

ALTERNATIVE EXPLANATIONS

By considering digoxin users as the reference group, we could have introduced a bias toward seeing a benefit of ACE inhibitors. Indeed, the role of digoxin in elderly persons and in women has not been tested; thus, we cannot exclude a priori a reduced efficacy or even a detrimental effect of digoxin in this study population. This hypothesis could be reinforced by the notion that elderly and cachectic patients are at increased risk of digoxin toxicity because of their lower total body muscle mass and often compromised renal function. Therefore, the results of the present study may show not that ACE inhibitors are beneficial but rather that digoxin should be avoided in these patients. The SAGE database does not include digoxin levels to conclusively refute this hypothesis. However, the patterns of digoxin use do not lend support to the hypothesis of a generalized adverse effect. In fact, we observed that nearly 85% of digoxin users were administered a 0.125-mg tablet daily, with an overall daily mean ± SD dose of 0.15 ± 0.07 mg and progressively lower dosage with increasing age (G.G., unpublished observations, 1998).

Another alternative explanation for our results rests on the evidence that the use of ACE inhibitors for CHF tends to be correlated with the training and experience of the physician. Patients who are cared for by cardiologists are more likely to receive ACE inhibitors and are more likely to receive them in effective doses. The overall care of patients taking ACE inhibitors and the ability of their physicians to deal with acute deterioration may be better. However, there is ample evidence that current treatment of old patients with CHF is less than optimal regardless. Only slightly more than 50% of patients hospitalized with CHF receive an ACE inhibitor, and similar findings have been documented in other settings, including nursing homes. The use of ACE inhibitors is significantly less in women and patients aged 70 years, and impaired renal function and fear of other side effects appear to be the most common disincentives. Moreover, the variables predicting the use of ACE inhibitor among patients with CHF in the SAGE database—previous hospitalization and admission in more recent years—did not differ among the 2 groups in the present analysis.

Finally, the possibility of confounding by indication needs to be carefully considered. That is, the 2 drugs—digoxin and ACE inhibitors—may be markers for distinct forms of CHF with differential mortality and morbidity. For example, among ACE inhibitors users there were twice as many hypertensive patients and this may suggest they had a higher ejection fraction. Conversely, digoxin use could be a marker of systolic dysfunction. This hypothesis can be refuted based on several lines of evidence. First, there is yet no indication of a protective effect of ACE inhibitors if ejection fraction is preserved and, indeed, such circumstance predicts their underprescription. Second, hypertension appears not to be a predictor of preserved ejection fraction. Third, stratifying patients on the basis of presence or absence of hypertension yielded almost identical results. Fourth, digoxin use is not a reliable marker of systolic dysfunction. Even at academic medical centers, as many as 26% of CHF patients with normal ejection fraction use digoxin, while only 57% of patients seen in geriatrics practice have appropriate indications for digoxin use.

Also, the possibility that digoxin users had an increased mortality as a result of a higher prevalence of atrial fibrillation seems unlikely. First, the arrhythmia has been found to be equally prevalent in patients with systolic or diastolic CHF. In addition, our stratified analysis has shown that ACE inhibitor therapy provided benefits regardless of the presence of atrial fibrillation.

LIMITATIONS

The most important limitation of the present study is the inability to distinguish systolic from diastolic heart failure. Ventricular function is most commonly assessed with Doppler echocardiography, but this technique remains greatly underused. Even at academic medical centers, 35% to 45% of patients hospitalized with CHF do not undergo assessment of ejection fraction, and in general practice only one third of patients with CHF undergo an echocardiogram. Yet, assessment of diastolic function is difficult, and the real utility of echocardiography is questioned because of the age-related variation in all the indices of diastolic performance.

Regardless, the patients included in the present study may be considered an ideal “model” of diastolic heart failure. In fact, in a similar population, as many as 75% to 80% of older CHF patients have some level of diastolic dysfunction. Moreover, Aronow et al.11 have determined that old age and female sex are the only independent predictors of diastolic dysfunction.
CONCLUSIONS

Our results suggest that even very old, frail, and clinically complex patients with CHF may benefit from ACE inhibitor therapy. This prolongs survival and reduces morbidity. Most notably, use of an ACE inhibitor is associated with a reduction in ADL decline that may translate into improved quality of life and, eventually, reduced health care costs. These findings need to be confirmed in prospective, randomized controlled clinical trials, but such trials are exceedingly difficult and expensive in very elderly, frail patients. Until then, ACE inhibitors should be considered in all patients with CHF who have no contraindications.

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