**Background:** β-Blockers have been shown to be beneficial in the treatment and prevention of heart failure (HF) in the general population, but they have not been assessed for their association with nonfatal HF in a nationally representative population of long-term dialysis patients.

**Methods:** We conducted a retrospective cohort study of 2550 patients enrolled in the US Renal Data System (USRDS) Wave 2 who were Medicare eligible at the start of the study. Analysis was stratified by the presence or absence of a known diagnosis of HF, and patients followed up until December 31, 2000. Cox regression analysis, including propensity scores, was used to model adjusted hazard ratios for β-blocker use (assessed separately by cardioselective activity and lipid solubility) with time to the first Medicare institutional claim for HF, cardiovascular-related death, or death from any cause.

**Results:** In patients without a previous history of HF, β-blocker use was significantly associated with a lower adjusted risk of HF (adjusted hazard ratio, 0.69; 95% confidence interval, 0.52-0.91; P=.008), with a similar reduction in risk of cardiac-related and all-cause death. β-Blocker use had no statistically significant associations with outcomes in patients with previous HF.

**Conclusions:** In dialysis patients without a previous documented history of HF, β-blocker use was associated with a lower risk of new HF, cardiovascular death, and death from any cause. No such associations were seen for dialysis patients with a previous history of HF. These results are hypothesis generating only and should be confirmed in randomized trials.

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**I N PATIENTS WITH SEVERE (STAGE 5) CHRONIC KIDNEY DISEASE, INCLUDING THOSE RECEIVING LONG-TERM DIALYSIS,** and those who have received kidney transplants, β-blockers have been shown to be beneficial in the treatment and prevention of heart failure (HF) in the general population, but they have not been assessed for their association with nonfatal HF in a nationally representative population of long-term dialysis patients. **Results:** In patients without a previous history of HF, β-blocker use was significantly associated with a lower adjusted risk of HF (adjusted hazard ratio, 0.69; 95% confidence interval, 0.52-0.91; P=.008), with a similar reduction in risk of cardiac-related and all-cause death. β-Blocker use had no statistically significant associations with outcomes in patients with previous HF.

**Conclusions:** In dialysis patients without a previous documented history of HF, β-blocker use was associated with a lower risk of new HF, cardiovascular death, and death from any cause. No such associations were seen for dialysis patients with a previous history of HF. These results are hypothesis generating only and should be confirmed in randomized trials.

Arch Intern Med. 2004;164:2465-2471
and Drug Administration in 1997 and, therefore, despite its ex-
ists, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibi-
60 of dialysis) were recorded in the DMMS Wave 2 database. From
medications prescribed to each patient at the study start date (day
containing binders was rare in the study population.
use of angiotensin II receptor blockers and aluminum-
sociation with HF, in accordance with established epidemi-
ables were set to the mean of the variable, and missing values
variables. Continuous variables that did not have a normal distri-
ment until the date of the first Medicare claim for HF during
the study, censored for death, date of renal transplantation, or
the end of the study.

STATISTICAL ANALYSIS

Univariate analysis was performed using the χ² test for cate-
egorical variables and the 2-tailed t test for continuous vari-
ables. Continuous variables that did not have a normal distri-
were set to the mean of the variable, and missing values
for categorical variables were presumed to be absent, as in pre-
vious investigations by the USRDS.20 For validation purposes,
analysis was also performed without interpolation of missing values for continuous variables. Analysis was also performed without censoring for the date of renal transplantation.

Variables with P<.10 in univariate analysis for a relation-
ship with development of a first Medicare claim for HF were
entered into multivariate analysis as covariates. An exception
was made for factors thought to have a clinical reason to be
associated with HF, in accordance with established epidemi-
logic principles.20 These factors included ACE inhibitor use,
calcium antagonist use, β-blocker use, body mass index, race,
sex, CHD, hematocrit value, and end-stage renal disease net-
work (to assess for regional differences).

Cox proportional hazards regression analysis was used to as-
ssess the association between baseline factors and time to HF, in-
dependent of other predictors. Formal and graphic methods were
used to verify the existence of proportional hazards. Because of
the nonrandomized nature of medication use, a propensity score
for use of β-blockers, calcium antagonists, and ACE inhibitors
was developed from logistic regression analysis of factors asso-
ciated with each medication. This score (in quartiles) was en-
tered into the Cox regression model. In addition, because of pos-
sible survival bias due to the use of death as a censoring point
for time to HF, a composite outcome of Medicare claims for HF
and death due to cardiovascular causes was also assessed in Cox
regression. Because BP is an independent risk factor for the de-
velopment of HF in the general population and in dialysis pa-
ients, and because antihypertensive and other medications are
underused among long-term dialysis patients, the use of spe-
cific agents was also analyzed, limited to patients taking β-block-
ers, ACE inhibitors, or calcium channel blockers.21

RESULTS

Of 4065 patients included in the DMMS Wave 2 cohort,
3621 had valid dates for starting dialysis in 1996. From this
cohort, 3374 patients had sufficient information to calcu-
late follow-up times, and of these, 2550 had confirmed Medi-
care eligibility 60 days after the start of dialysis. Table 1 gives
the characteristics of the study population, stratified by pa-
ients with and without a documented history of HF within
10 years of the start of the study.

In unadjusted analysis of factors associated with de
ovo HF, aspirin was the only medication significantly
associated with HF. Other factors significant in unad-
justed analysis were older age, diabetes mellitus, history

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Patients With Previous HF

Table 1. Selected Factors Assessed in Patients With ESRD Who Had Medicare as the Primary Payer at Day 60, DMMS Wave 2, 1996

<table>
<thead>
<tr>
<th>Demographic factors</th>
<th>Hospitalized for HF (n = 549)</th>
<th>Not Hospitalized for HF (n = 1029)</th>
<th>Hospitalized for HF (n = 528)</th>
<th>Not Hospitalized for HF (n = 348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No. (%)</td>
<td>308 (56.1)</td>
<td>581 (56.5)</td>
<td>290 (54.9)</td>
<td>193 (55.5)</td>
</tr>
<tr>
<td>African American, No. (%)</td>
<td>145 (26.4)</td>
<td>312 (30.3)</td>
<td>109 (20.6)</td>
<td>77 (22.1)</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>60.1 ± 15†</td>
<td>52.5 ± 16</td>
<td>66.3 ± 11.3</td>
<td>64.0 ± 13.9</td>
</tr>
<tr>
<td>Body mass index, mean ± SD, kg/m²‡</td>
<td>26.5 ± 5.8</td>
<td>26.4 ± 5.9</td>
<td>26.6 ± 5.9</td>
<td>26.2 ± 6.4</td>
</tr>
<tr>
<td>Putative cardiovascular factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-phosphorus double product, mean ± SD, mg/dL</td>
<td>48.8 ± 25.5</td>
<td>50.2 ± 31.4</td>
<td>47.7 ± 32.7</td>
<td>50.6 ± 52.5</td>
</tr>
<tr>
<td>Total cholesterol, mean ± SD, mg/dL</td>
<td>197.9 ± 50.8</td>
<td>194.4 ± 52.9</td>
<td>187 ± 52.4</td>
<td>189.3 ± 52.0</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>242 (44.1)§</td>
<td>368 (35.8)</td>
<td>329 (62.3)</td>
<td>214 (61.5)</td>
</tr>
<tr>
<td>History of coronary heart disease, No. (%)</td>
<td>146 (26.6)§</td>
<td>172 (16.7)</td>
<td>354 (67.0)</td>
<td>208 (59.8)</td>
</tr>
<tr>
<td>Peripheral vascular disease, No. (%)</td>
<td>73 (13.3)§</td>
<td>89 (8.6)</td>
<td>140 (26.5)</td>
<td>99 (28.4)</td>
</tr>
<tr>
<td>LVH by chest radiography, No. (%)</td>
<td>101 (18.4)§</td>
<td>138 (13.4)</td>
<td>240 (45.5)</td>
<td>142 (40.8)</td>
</tr>
<tr>
<td>LVH by electrocardiography, No. (%)</td>
<td>70 (12.8)§</td>
<td>95 (9.2)</td>
<td>103 (19.5)</td>
<td>83 (23.6)</td>
</tr>
<tr>
<td>Smoking, No. (%)</td>
<td>33 (6.0)§</td>
<td>195 (19.0)</td>
<td>48 (9.1)</td>
<td>23 (6.6)</td>
</tr>
<tr>
<td>Predialysis systolic BP, mean ± SD, mm Hg</td>
<td>149.1 ± 24.3‡</td>
<td>145.9 ± 23.3</td>
<td>149.2 ± 25.7</td>
<td>145.7 ± 27.2</td>
</tr>
<tr>
<td>Predialysis diastolic BP, mean ± SD, mm Hg</td>
<td>79.9 ± 13.7</td>
<td>82.5 ± 14.1</td>
<td>76.5 ± 14.3</td>
<td>76.7 ± 14.8</td>
</tr>
<tr>
<td>Predialysis pulse pressure, mean ± SD, mm Hg</td>
<td>69.3 ± 19.7†</td>
<td>63.5 ± 19.6</td>
<td>72.7 ± 20.2</td>
<td>69.0 ± 20.3</td>
</tr>
<tr>
<td>Hematocrit, mean ± SD, %</td>
<td>30.3 ± 6.4</td>
<td>30.4 ± 6.5</td>
<td>31.0 ± 5.6</td>
<td>30.9 ± 6.9</td>
</tr>
<tr>
<td>Chronic kidney disease–specific factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin, mean ± SD, g/dL</td>
<td>3.5 ± 0.6</td>
<td>3.5 ± 0.6</td>
<td>3.4 ± 0.5</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>Hemodialysis, No. (%)</td>
<td>285 (51.9)§</td>
<td>416 (40.4)</td>
<td>305 (57.8) §</td>
<td>174 (50.0)</td>
</tr>
<tr>
<td>Medications, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers (yes) /†الفحص Describe the relationship between medications for the development of a propensity score and the factors associated with previous HF.</td>
<td>94 (17.1)</td>
<td>204 (19.8)</td>
<td>106 (20.1)</td>
<td>70 (20.1)</td>
</tr>
<tr>
<td>Cardioselective</td>
<td>70 (12.8)</td>
<td>145 (14.1)</td>
<td>85 (16.1)</td>
<td>53 (15.2)</td>
</tr>
<tr>
<td>Noncardioselective</td>
<td>26 (4.7)</td>
<td>63 (6.1)</td>
<td>24 (4.5)</td>
<td>18 (5.2)</td>
</tr>
<tr>
<td>Non–lipid soluble (renaly excreted)</td>
<td>29 (5.3)</td>
<td>60 (5.8)</td>
<td>26 (4.9)</td>
<td>23 (6.6)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>233 (51.5)</td>
<td>545 (53.0)</td>
<td>245 (46.4)</td>
<td>172 (49.4)</td>
</tr>
<tr>
<td>Dihydropyridine</td>
<td>218 (39.7)</td>
<td>408 (39.7)</td>
<td>193 (36.6)</td>
<td>141 (40.5)</td>
</tr>
<tr>
<td>Non-dihydropyridine</td>
<td>72 (13.1)†</td>
<td>144 (14.0)</td>
<td>55 (10.4)</td>
<td>32 (9.2)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>123 (22.4)</td>
<td>244 (23.7)</td>
<td>135 (25.6)</td>
<td>76 (21.8)</td>
</tr>
<tr>
<td>Statins</td>
<td>50 (9.1)</td>
<td>93 (9.0)</td>
<td>52 (9.8)§</td>
<td>20 (5.7)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12 (2.2)§</td>
<td>10 (1.0)</td>
<td>12 (3.8)</td>
<td>21 (6.0)</td>
</tr>
<tr>
<td>Aspirin (yes)</td>
<td>101 (18.4)†</td>
<td>143 (13.9)</td>
<td>141 (28.7)</td>
<td>77 (22.1)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; BP, blood pressure; DMMS, Dialysis Morbidity and Mortality Study; ESRD, end-stage renal disease; HF, heart failure (International Classification of Disease, Ninth Revision, code 423.x); LVH, left ventricular hypertrophy.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; cholesterol to millimoles per liter, multiply by 0.0259; phosphorous to millimoles per liter, multiply by 0.323.

*Of the study cohort, 96 patients (3.8%) were missing data for preexisting HF and were excluded from this study.
†P < .01 by 2-tailed t test vs patients not hospitalized for HF.
‡Based on the average of 3 postdialysis weights because more information was available for predialysis than postdialysis weights.
§P < .05 by χ² test vs patients not hospitalized for HF.
¶Combination use of medications was common. Of all study patients, 10.7% (n=316) used β-blockers and calcium channel blockers concomitantly, 4.0% (n=117) used β-blockers and ACE inhibitors concomitantly, and 10.6% (n=313) used calcium channel blockers and ACE inhibitors concomitantly.
*Cardioselective β-blockers were considered to be acebutolol, atenolol, beta-blockers hydrochloride, bisoprolol, esmolol hydrochloride, metoprolol, and practolol. Although β-blockers exhibit a spectrum of lipid solubility, in this analysis, non–lipid-soluble β-blockers were considered to be atenolol, nadolol, and timolol.
β-Blockers with intrinsic sympathomimetic activity include acebutolol, alpenrolol hydrochloride, carteolol hydrochloride, exprenolol hydrochloride, penbutolol sulfate, pindolol, and practolol. However, other than acebutolol and pindolol, their use was infrequent in this cohort and was not sufficient for analysis.

of CHD, presence of left ventricular hypertrophy (on either chest radiographs or electrocardiograms), elevated systolic BP and pulse pressure, and hemodialysis (vs peritoneal dialysis). The only 2 factors associated with recurrent HF were hemodialysis and use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

Logistic regression analysis of factors independently associated with medications for the development of a propensity score revealed that the following factors were independently associated with use of β-blockers: previous CHD, peritoneal dialysis (vs hemodialysis), higher systolic BP, aspirin use, and lower use in patients with diabetes mellitus. Previous HF was not significantly associated with use of β-blockers (20.1% β-blocker use in patients with known HF vs 18.9% in patients without known HF; P = .47 by χ² test), and the adjusted odds ratio for β-blocker use in patients with known HF was 0.95 (95% confidence interval, 0.68-1.32; P = .76 by logistic regression). Only 2 factors were significantly associated with ACE inhibitor use: older age (P < .001) and diabetes mellitus (P = .001). Use of calcium channel blockers was independently associated with peritoneal dialysis, smoking, higher serum albumin levels, African American race, and higher systolic BPs.
Use of β-blockers was independently associated with a lower risk of de novo HF; among subtypes of β-blockers, cardioselective β-blockers were statistically significant and noncardioselective β-blockers (which were also used much less frequently) were not; use of β-blockers and aspirin together, however, was associated with an increased risk of HF (Table 2). Other factors significantly associated with de novo HF in adjusted analysis were older age, diabetes mellitus, hemodialysis (vs peritoneal dialysis), and lower serum albumin levels. The decreased risk of HF associated with β-blocker use was proportional over time (as assessed by formal and graphical methods), although by visual inspection there was some disparity in unadjusted risk of HF in the first year by β-blocker use, after which the risk of HF was similar (Figure 1).

Analysis of composite outcomes of HF and cardiovascular death produced similar findings, except that individual classes of β-blockers were not statistically significant (Table 3). Figure 2 shows the results of Cox regression analysis limited to specific subgroups. β-Blocker use was independently associated with a lower risk of de novo HF, a composite outcome of HF and cardiovascular death, and all-cause death, even in models limited to patients taking β-blockers, ACE inhibitors, or calcium channel blockers. β-Blocker use retained its statistical significance even in adjusted models limited to patients with or without diabetes mellitus, CHD, or hemodialysis/peritoneal dialysis, although the number of diabetic patients in whom noncardioselective β-blockers were used was insufficient to calculate hazard ratios. Use of ACE inhibitors was not associated with de novo HF, cardiovascular death, or all-cause death in dialysis patients who did not have known HF.

Factors independently associated with recurrent HF are given in Table 4. Aspirin use was associated with an increased risk of recurrent HF, whereas use of calcium channel blockers was associated with a reduced risk of recurrent HF. Other factors included older age and history of CHD. β-Blocker use was not statistically significantly associated with recurrent HF, composite HF and cardiovascular death, or all-cause death in this subgroup, including stratification by subgroups.

### Table 2. Cox Regression Analysis of Factors Associated With De Novo Heart Failure

<table>
<thead>
<tr>
<th>Medication use</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers*</td>
<td>0.69 (0.52-0.91)</td>
<td>.008</td>
</tr>
<tr>
<td>Cardioselective</td>
<td>0.67 (0.51-0.91)</td>
<td>.009</td>
</tr>
<tr>
<td>Noncardioselective</td>
<td>0.85 (0.55-1.31)</td>
<td>.46</td>
</tr>
<tr>
<td>β-Blockers and aspirin</td>
<td>1.79 (1.06-3.01)</td>
<td>.03</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.02 (0.70-1.49)</td>
<td>.90</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>0.94 (0.77-1.15)</td>
<td>.54</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>0.97 (0.76-1.23)</td>
<td>.80</td>
</tr>
</tbody>
</table>

### Table 3. Cox Regression Analysis of Time to Either De Novo Heart Failure or Cardiac Death (Composite)

<table>
<thead>
<tr>
<th>Medication use</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>0.59 (0.43-0.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardioselective</td>
<td>1.10 (0.77-1.57)</td>
<td>.62</td>
</tr>
<tr>
<td>Noncardioselective</td>
<td>0.95 (0.70-1.30)</td>
<td>.75</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>0.95 (0.80-1.15)</td>
<td>.56</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>0.91 (0.74-1.13)</td>
<td>.40</td>
</tr>
</tbody>
</table>

### Figure 1. Kaplan-Meier plot of unadjusted time to Medicare institutional claims for de novo heart failure (HF) (International Classification of Diseases, Ninth Revision, code 428.x) by use or nonuse of β-blockers 60 days or more after the start of dialysis in patients with Medicare as the primary payer at day 60, United States Renal Data System Morbidity and Mortality Study Wave 2 cohort, excluding patients with a known diagnosis of HF. Time to de novo chronic heart failure was significantly longer for use of β-blockers, P=.007 by the log rank test.

### Figure 2. Kaplan-Meier plot of unadjusted time to Medicare institutional claims for de novo heart failure (HF) (International Classification of Diseases, Ninth Revision, code 428.x) by use or nonuse of β-blockers 60 days or more after the start of dialysis in patients with Medicare as the primary payer at day 60, United States Renal Data System Morbidity and Mortality Study Wave 2 cohort, excluding patients with a known diagnosis of HF. Time to de novo chronic heart failure was significantly longer for use of β-blockers, P=.007 by the log rank test.

### Figure 3. Kaplan-Meier plot of unadjusted time to Medicare institutional claims for de novo heart failure (HF) (International Classification of Diseases, Ninth Revision, code 428.x) by use or nonuse of β-blockers 60 days or more after the start of dialysis in patients with Medicare as the primary payer at day 60, United States Renal Data System Morbidity and Mortality Study Wave 2 cohort, excluding patients with a known diagnosis of HF. Time to de novo chronic heart failure was significantly longer for use of β-blockers, P=.007 by the log rank test.

### Figure 4. Kaplan-Meier plot of unadjusted time to Medicare institutional claims for de novo heart failure (HF) (International Classification of Diseases, Ninth Revision, code 428.x) by use or nonuse of β-blockers 60 days or more after the start of dialysis in patients with Medicare as the primary payer at day 60, United States Renal Data System Morbidity and Mortality Study Wave 2 cohort, excluding patients with a known diagnosis of HF. Time to de novo chronic heart failure was significantly longer for use of β-blockers, P=.007 by the log rank test.

### Figure 5. Kaplan-Meier plot of unadjusted time to Medicare institutional claims for de novo heart failure (HF) (International Classification of Diseases, Ninth Revision, code 428.x) by use or nonuse of β-blockers 60 days or more after the start of dialysis in patients with Medicare as the primary payer at day 60, United States Renal Data System Morbidity and Mortality Study Wave 2 cohort, excluding patients with a known diagnosis of HF. Time to de novo chronic heart failure was significantly longer for use of β-blockers, P=.007 by the log rank test.
all-cause death. β-Blockers were used by only 20% of patients in this cohort regardless of the presence of previous HF. Studies in the general population suggest that, at most, 70% of high-risk patients can tolerate β-blockers, even under optimal conditions. Therefore, the use of β-blockers in dialysis patients seems far lower than would seem appropriate. Furthermore, the association of β-blocker use with de novo HF and survival persisted even when limited to patients who were taking β-blockers, ACE inhibitors, or calcium channel blockers, independent of measures of BP control, which is suboptimally treated in this population. The association with outcomes was more pronounced in terms of statistical significance and reduction of risk for cardioselective β-blockers. Cardioselective β-blockers are also less prone to peripheral vasodilation and, perhaps most important, have a lower risk of hyperkalemia than noncardioselective β-blockers, which may partly explain why they were used more frequently than noncardioselective β-blockers.

Given the observational nature of this study, we cannot entirely exclude bias in indication for the use of β-blockers, namely, that β-blockers were withheld from patients perceived to be at the highest risk of HF or death, which could have yielded the same results. In logistic regression analysis of factors associated with β-blocker use, β-blocker use, age, race, sex, diabetes mellitus status, coronary heart disease status, quartiles of serum albumin concentration, dialysis modality, pulse pressure, aspirin use, angiotensin-converting enzyme inhibitor use, calcium channel blocker use, and left ventricular hypertrophy by chest radiography for de novo heart failure or composite outcomes by use of β-blockers: Medicare claims for HF for all patients without previous HF with and without both diabetes and CHD (D), adjusted HRs for the composite outcome of HF and all-cause death, limited to patients without previous HF (E). CS indicates cardioselective; asterisk, P<.05 by Cox regression; dagger, insufficient numbers to calculate. Error bars represent 95% confidence intervals. For E, 1 indicates composite outcome of claims for de novo HF of cardiovascular death; 2, cardiovascular death only; and 3, all-cause death.
ers were used more frequently in patients with known CHD but less frequently in patients with diabetes mellitus, although both are known risk factors for mortality. Diabetes mellitus was more common but not as strongly associated with mortality as CHD. We used multiple methods, including adjustment, stratification, propensity scores, and multiple outcomes, to account for baseline differences in patient characteristics, and the statistical significance of β-blockers was robust in all these analyses. From a clinical point of view, it is not clear why β-blocker use would be “reserved” for healthier or low-risk patients in this population, other than its relative avoidance in patients with diabetes mellitus; in fact, just the opposite is more likely, because β-blocker use is preferentially recommended for patients with known CHD, and use of β-blockers is often avoided in patients with high expectations of physical exercise or sexual function, usually markers of better health, which the present study could not measure. Of course, only randomized controlled trials could exclude the possibility of residual confounding.

In contrast to de novo HF, the lack of apparent benefit of β-blocker use in patients with established HF in the present study is rather striking. Studies in the general population have found that the survival benefit associated with β-blocker use was similar regardless of the degree of severity of HF. However, Foley et al reported in a prospective cohort study of dialysis patients that conventional risk factors (hypertension, anemia, serum albumin level, and mode of dialysis) corresponded with left ventricular enlargement during the first year of therapy but were no longer significant during the second through fourth years, suggesting that intervention after the first year of dialysis (or perhaps in patients with established cardiomyopathy) might be relatively less effective. In that cohort approximately one third of the patients were taking β-blockers, but no specific medication was associated with changes in cardiac enlargement over time. Theoretical disadvantages of β-blockers, such as effects on arterial compliance (which may, in part, be class specific), may thus be relatively more important in patients with established HF. Whether advantages reported for carvedilol compared with other β-blockers are independent of differences in dosing regimens is controversial. However, although β-blocker use in general may reduce cardiovascular risk in patients with stage 5 chronic kidney disease, carvedilol is the one thus far with data from a randomized trial documenting this relationship. Calcium channel blockers, in particular those of the dihydropyridine class, which do not have known beneficial effects on neurohormonal activity in HF, were associated with a reduced risk of recurrent HF, analogous to their association with all-cause and cardiovascular mortality reported previously.

Aspirin use was associated with an increased risk of recurrent HF in dialysis patients, a finding that our group discussed previously. A recent randomized controlled trial indicated that use of aspirin was associated with higher risk of recurrent hospitalized HF in patients with prevalent HF, a risk that was independent of prevalent CHD. Results of recent preliminary studies indicate that this association may be related to adverse effects of aspirin on arterial stiffness, at least at dosages of 325 mg/d. To quote a recent review, COX inhibitors may therefore be deleterious in cardiovascular disease and/or counteract part of ACE inhibitor (ACE-I) efficacy. This has been clearly demonstrated with non-steroidal anti-inflammatory drugs (NSAIDs), including high-dose aspirin, in hypertension, coronary artery disease and chronic heart failure (CHF); most guidelines recommend avoiding their use in such patients.

An adverse effect of aspirin use on survival in patients with established HF has not been demonstrated. Although use of nonsteroidal anti-inflammatory agents is discouraged in patients with HF, most expert recommendations do not discourage the use of low-dose aspirin (<100 mg/d) in patients who also use ACE inhibitors. We are not aware of any reported interactions between β-blockers and aspirin in association with incident HF.

The limitations of the present analysis have been discussed in depth in a previous article, but, in addition, the use of medications in a retrospective cohort analysis is prone to potential bias. Despite using multiple methods to address this potential bias, we cannot exclude the possibility of residual confounding. We could not assess medication adverse effects or changes in medication use after the start of the study. Use of International Classification of Diseases, Ninth Revision, codes, in particular code 428.x, for outcomes may underestimate the true incidence of HF in this population. However, among dialysis patients, other codes, such as “volume overload,” may have different implications than in the general population and so were not used in this analysis. Misclassification of events is also possible because diagnoses could not be verified. The analysis of recurrent HF, in contrast to de novo HF, was, in essence, a cross-sectional study of survival of previous HF episodes, and the severity and recency of HF could not be assessed. Ideally, patients with HF would be followed up from the time of their first HF event, an approach not possible in this study. Use of quartiles for propensity scores could have resulted in residual confounding. In any case, retrospective, nonrandomized analyses cannot prove causation but can suggest hypotheses to be tested in prospective trials and can provide useful information on potential sample size requirements, effect size, and possible confounders.

In summary, the present retrospective analysis demonstrates that use of β-blockers was independently as-

| Table 4. Cox Regression Analysis of Factors Associated With Recurrent Heart Failure |
|---------------------------------|-----------------|--------|
| Medication use                  | Adjusted HR (95% CI) | P Value |
| Aspirin                         | 1.27 (1.01-1.59)    | .04    |
| Calcium channel blockers        | 0.67 (0.55-0.81)    | <.001  |
| Dihydropyridine                 | 0.67 (0.55-0.82)    | <.001  |
| Nondihydropyridine              | 0.79 (0.56-1.10)    | .16    |
| β-Blockers                      | 1.11 (0.83-1.49)    | .48    |
| Other covariates                |                   |        |
| Older age (per 10 y)            | 1.31 (1.20-1.42)    | <.001  |
| Previous coronary heart disease (in past 10 y) | 1.31 (1.05-1.64)    | .02    |

Abbreviations: CI, confidence interval; HR, hazard ratio.
associated with a reduced risk of incident HF and cardiovascular-related and all-cause death in long-term dialysis patients who did not have a known diagnosis of HF at the time of dialysis initiation. Together with the findings of previous studies in this same cohort, the results of the present study also suggest that different medications may have different associations with outcomes based on a previous diagnosis of heart disease, with implications for research and clinical practice. Because of the potential limitations of this analysis, it would be premature for clinicians to withhold β-blockers from patients with end-stage renal disease and a history of HF.

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Author Affiliations: Nephrology (Drs Abbott, Trespalacios, Agodoa, and Bakris) and Cardiology (Dr Taylor) Services, Walter Reed Army Medical Center, Washington, DC; Divisions of Nephrology (Dr Abbott) and Cardiology (Dr Taylor), Uniformed Services University of the Health Sciences, Bethesda, Md; Nephrology Service, Madigan Army Medical Center, Ft Lewis, Wash (Dr Trespalacios); National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Md; Nephrology Service, Massachusetts General Hospital, Boston, Mass (Dr Trespalacios); National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda (Dr Agodoa); and Preventive Medicine Service, Rush Presbyterain Medical Center, Chicago, Ill (Dr Bakris).

Correspondence: LTC(P) Kevin C. Abbott, MC, USA, Nephrology Service, Walter Reed Army Medical Center, Washington, DC 20307-5001 (kevin.abbott@na.meddy.army.mil).

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