Objectives
The aim of this systematic review was to study the benefits and risks of beta-adrenergic antagonists (beta-blockers) in patients with chronic kidney disease (CKD).

Background
There is an excess burden of cardiovascular disease and death in people with CKD. Despite their potential benefits, the effects of beta-blockers in this population are uncertain.

Methods
CENTRAL (Cochrane Central Register of Controlled Trials), Medline (Medical Literature Analysis and Retrieval System Online), and Embase (Excerpta Medical Database) were searched for randomized controlled trials with at least 3 months of follow-up in patients with CKD stages 3 to 5 that reported mortality outcomes. Summary estimates of effect were obtained using a random effects model.

Results
Eight trials met criteria for review: 6 placebo-controlled trials involving 5,972 participants with chronic systolic heart failure and 2 angiotensin-converting enzyme inhibitor-comparator trials involving 977 participants not known to have heart failure. In CKD patients with heart failure, compared with placebo, beta-blocker treatment reduced the risk of all-cause (risk ratio [RR]: 0.72, 95% confidence interval [CI]: 0.64 to 0.80) and cardiovascular mortality (RR: 0.66, 95% CI: 0.49 to 0.89), but increased the risk of bradycardia (RR: 4.92, 95% CI: 3.20 to 7.55) and hypotension (RR: 5.08, 95% CI: 3.48 to 7.41). Quantitative meta-analysis was not performed for the non-heart failure studies due to substantial clinical diversity or lack of informative data.

Conclusions
Treatment with beta-blockers improved all-cause mortality in patients with CKD and chronic systolic heart failure. There is insufficient evidence to conclude whether people with CKD who are not known to have heart failure derive benefit from beta-blockers. (J Am Coll Cardiol 2011;58:1152–61) © 2011 by the American College of Cardiology Foundation
Chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) reduced to <60 ml/min/1.73 m² or excess proteinuria (≥250 mg/day or urine albumin-creatinine ratio ≥30 mg/g), is a major public health problem affecting 8% to 12% of adults in industrialized countries (1,2). Compared with the general population, people with CKD, including those receiving dialysis, are at greater risk of death (3–5). A cardiac cause accounts for 35% to 40% of all deaths in patients with end-stage renal disease on dialysis (6–8). In CKD patients who are not yet on dialysis (nondialysis CKD patients), the risk of having a cardiovascular event is inversely proportional to eGFR (3,4,9–12). Results of a collaborative meta-analysis of general population cohorts consisting of more than 1.2 million people showed that eGFR <60 ml/min/1.73 m² was an independent predictor of all-cause and cardiovascular mortality (13). Furthermore, there was an exponential increase in the risk of death at lower eGFR levels.

Beta-adrenergic receptor antagonists ("beta-blockers") reduce mortality in patients following myocardial infarction and in patients with chronic systolic heart failure (14,15). Evidence-based treatment guidelines recommend their use in such patients unless contraindicated or not tolerated (16,17). However, randomized controlled trials (RCTs) providing this evidence have generally excluded individuals with CKD, including end-stage renal disease patients requiring dialysis (18,19). Ischemic heart disease, congestive heart failure, arrhythmias, left ventricular hypertrophy, and increased sympathetic nervous system activity are highly prevalent in people with advanced CKD, and this population could theoretically derive large benefits from beta-blockers (7,8,20–25).

Observational studies in patients with CKD have demonstrated better survival and cardiovascular outcomes in those treated with beta-blockers (26–28). Despite this, the use of beta-blockers in patients receiving dialysis varies considerably, ranging from as few as 10% of patients in Japan to approximately 60% in the United States (29,30). In a study of nondialysis CKD patients who had a myocardial infarction, the frequency of beta-blocker use diminished as eGFR declined (3). In the United States, 61% and 73% of all dialysis patients with congestive heart failure and acute myocardial infarction, respectively, were prescribed beta-blockers (30). The variable rates of utilization of beta-blockers in dialysis patients may be due to uncertainty regarding potential benefits in this population, as well as the possibility of hemodynamic side effects in patients subjected to wide fluctuations in extracellular fluid volume. Several investigators have called for an increased use of beta-blockers in dialysis patients while awaiting RCTs (31–34).

Therefore, the aim of this systematic review was to determine the effects of beta-blockers on clinical endpoints in patients with CKD stages 3 to 5 including those on dialysis.

Methods

A systematic review was undertaken in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement (35).

Search strategy, study selection, and data extraction. Studies were eligible for inclusion if they: 1) were randomized controlled trials; 2) included participants with CKD stages 3 to 5 (eGFR ≤60 ml/min/1.73 m²), including those on dialysis therapy, who were randomized to an oral beta-blocking agent compared with placebo, a cardiovascular agent of another class, or no treatment; 3) followed patients for at least 3 months post-randomization; and 4) reported mortality outcomes. Trials performed in kidney transplant patients were excluded.

Relevant studies were identified through electronic searches of Medline (Medical Literature Analysis and Retrieval System Online) via Ovid (from inception to October 2010), Embase (Excerpta Medical Database) (from inception to October 2010), and the CENTRAL (Cochrane Central Register of Controlled Trials) (Issue 4, 2010) without any language restriction. In addition, reference lists of relevant review articles, systematic reviews, treatment guidelines, textbook chapters, conference proceedings, and online trial registries were searched. Missing, incomplete, or unpublished data from clinical trials were requested from the respective investigators/authors by e-mail. (See the Online Appendix for complete search strategy.)

The following data were extracted using a standardized form: patient demographic details, study design and conduct, rates of outcome events, and adverse events. The methodological quality of each included study was assessed using the risk of bias assessment tool developed by the Cochrane Bias Methods Group (36). The following 6 items were assessed: 1) random sequence generation; 2) allocation concealment; 3) blinding; 4) incomplete outcome data; 5) selective outcome reporting; and 6) any other bias (e.g., insufficient rationale, study design).

Outcomes assessed. The primary outcome assessed in this meta-analysis was all-cause mortality. In addition, all other reported clinical outcomes such as cardiovascular mortality, sudden death, all-cause hospitalization, hospitalization for worsening of heart failure, and adverse events were assessed.

Statistical analysis. For dichotomous outcomes, the results were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Summary estimates were obtained by ran-
dom effects model using the DerSimonian and Laird method (37). Heterogeneity across the studies was estimated using the I-square test (38). I-square values of 25%, 50%, and 75% correspond to low, moderate, and high levels of heterogeneity (39). Meta-analysis results were reported only if the I-square value was lower than 75%. We analyzed trials that only included participants with “heart failure” separately to those with a broader range of participants (“non–heart failure” studies) because there were substantial differences in cardiovascular morbidity, comparator, and duration of follow-up. If sufficient data were available, subgroup analysis was performed according to severity of kidney disease (nondialysis CKD and end-stage renal disease requiring dialysis). The statistical analyses were done with Stata/SE (version 10.1, Stata Corp., College Station, Texas).

Results

Selection and description of studies. Nine reports of 8 trials involving 6,949 patients were included in the systematic review (Fig. 1). Six trials were performed in 5,972 patients with chronic systolic heart failure (40–44). Data from 2 of these trials were obtained from a previously published patient-level meta-analysis (44). Data on the number of events in the individual trial arms were not available in 1 report (43) and, hence, were extracted from the previous publication of the same trial (45). The remaining 2 trials were conducted in 977 patients without heart failure (46,47) (Table 1). One additional trial included patients receiving dialysis and reported clinical endpoints in abstract form (48), but we were unable to obtain the necessary data required for inclusion.

Patients undergoing dialysis were included in only 1 of 6 chronic systolic heart failure studies (114 patients, all on hemodialysis) (40). The remaining 5 trials were post hoc analyses reporting on the subgroup of nondialysis CKD patients within a larger study evaluating beta-blockers in patients with chronic systolic heart failure (41–44). One of these trials was restricted to elderly patients (age >70 years) (41). The major distinction from the non–heart failure studies was that all 6 trials compared a beta-blocker with a placebo.

None of the 2 non–heart failure studies included dialysis patients (Table 1) (46,47). A beta-blocker was used as an active comparator to an angiotensin-converting enzyme inhibitor in both of these trials, which had a primary objective to study the effect of an angiotensin-converting enzyme inhibitor on the progression of CKD (46,47).
## Table 1 Characteristics of Included Studies

<table>
<thead>
<tr>
<th>First Author (Study)</th>
<th>Inclusion Criteria</th>
<th>n</th>
<th>Active Treatment</th>
<th>Control</th>
<th>LVEF (%)</th>
<th>GFR* or Type of Dialysis, Mean (SD)</th>
<th>Follow-Up</th>
<th>Age (yrs), Mean (SD)</th>
<th>Men (%)</th>
<th>DM (%)</th>
<th>MI (%)</th>
<th>Concomitant ACE Inhibition (%)</th>
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<td><strong>Heart Failure Studies</strong></td>
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<td>Cice (39,48) (Italy)</td>
<td>ESRD LVEF &lt; 35%</td>
<td>114</td>
<td>Carvedilol (3.125–25 mg BD)</td>
<td>Placebo</td>
<td>26 (8)</td>
<td>All HD</td>
<td>24 months</td>
<td>55 (7.6)</td>
<td>62</td>
<td>NR</td>
<td>70</td>
<td>100</td>
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<td>Symptomatic heart (NYHA II–III)</td>
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<td>Castagno (CIBIS-II) (42,44) (Multinational)</td>
<td>GFR* ≤60 LVEF &lt; 35%</td>
<td>1,119</td>
<td>Bisoprolol (1.25–10 mg daily)</td>
<td>Placebo</td>
<td>NR</td>
<td>NR</td>
<td>1.3 yrs</td>
<td>NR</td>
<td>66</td>
<td>14</td>
<td>70</td>
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<td>Symptomatic heart failure (NYHA III–IV)</td>
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<tr>
<td>Ghali (MERIT-HF) (41) (Multinational)</td>
<td>GFR* ≤60 LVEF &lt; 40%</td>
<td>1,469</td>
<td>Metoprolol CR/XL (25–200 mg daily)</td>
<td>Placebo</td>
<td>27 (7)</td>
<td>47.7 (9.5)</td>
<td>1 yr</td>
<td>68.1 (8.2)</td>
<td>68</td>
<td>29</td>
<td>55</td>
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<td>Symptomatic heart failure (NYHA II–IV)</td>
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<tr>
<td>Cohen-Solal (SENIORS) (40) (Multinational)</td>
<td>GFR* ≤60 Age &gt; 70 yrs</td>
<td>704</td>
<td>Nebivolol (1.25–10 mg daily)</td>
<td>Placebo</td>
<td>34.2 (12.1)</td>
<td>43.5 (8.9)</td>
<td>21 months</td>
<td>77.4 (5)</td>
<td>59</td>
<td>29</td>
<td>46</td>
<td>NR</td>
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<td></td>
<td>Symptomatic heart failure (NYHA II–IV) defined as LVEF &lt; 35% or prior hospitalization for heart failure in the previous year</td>
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<tr>
<td>Wali (Pooled data from CAPRICORN and COPERNICUS trials) (43)</td>
<td>GFR* ≤60 CAPRICORN trial: Symptomatic heart failure Post-acute MI</td>
<td>2,566</td>
<td>CAPRICORN trial: Carvedilol (6.25–25 mg BD)</td>
<td>Placebo</td>
<td>24 (8)</td>
<td>45.5 (9.6)</td>
<td>13 months</td>
<td>65.7 (10.5)</td>
<td>71</td>
<td>26</td>
<td>15</td>
<td>99</td>
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<td></td>
<td>COPERNICUS trial: Symptomatic or asymptomatic heart failure LVEF &lt; 25%</td>
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<td>Hannedouche (46) (France)</td>
<td>Creatinine 200–400 μmol/l</td>
<td>100</td>
<td>Acebutolol (400 mg daily) or atenolol (100 mg daily)</td>
<td>Enalapril (5–10 mg daily)</td>
<td>NR</td>
<td>Inulin clearance 25.7 (10.5)</td>
<td>3 yrs</td>
<td>51 (2.2)</td>
<td>53</td>
<td>Ex</td>
<td>Ex</td>
<td>NA</td>
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<tr>
<td>Wright (AASK) (45) (United States)</td>
<td>GFR* 20 to 65 Hypertensive</td>
<td>877</td>
<td>Metoprolol (50–200 mg/day)</td>
<td>Ramipril (2.5–10 mg/day)</td>
<td>NR</td>
<td>45.6 (13.1)</td>
<td>4.1 yrs</td>
<td>54.7 (10.6)</td>
<td>61</td>
<td>Ex</td>
<td>NR</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Expressed as ml/min/1.73 m². †Expressed as median (interquartile range).

AASK = African American Study of Kidney Disease and Hypertension; ACE = angiotensin-converting enzyme; BD = twice daily; CAPRICORN = Carvedilol Post-Infarct Survival Controlled Evaluation; CIBIS-II = The Cardiac Insufficiency Bisoprolol Study II; COPERNICUS = Effect of Carvedilol on Survival in Severe Chronic Heart Failure; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESRD = end-stage kidney disease; Ex = excluded; GFR = glomerular filtration rate; HD = hemodialysis; LVEF = left ventricular ejection fraction; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial In Congestive Heart Failure; MI = myocardial infarction; NA = not applicable; NR = not reported; NYHA = New York Heart Association; SENIORS = Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure.
Figure 2 summarizes the risk of bias assessment of the individual studies. Allocation concealment was adequate in only 4 trials. The only trial involving dialysis patients with heart failure was a double-blind protocol during the initial 12 months (40), but became an open-label protocol after 12 months, and the investigators reported mortality after the second 12-month period in a subsequent publication (49).

**Effects of intervention.** **HEART FAILURE STUDIES.** Compared with placebo, treatment with beta-blockers reduced the risk of all-cause mortality (6 trials; risk ratio [RR]: 0.72, 95% confidence interval [CI]: 0.64 to 0.80, p < 0.001; test for heterogeneity I-square = 0%, p = 0.601) (Fig. 3). The p values testing for an interaction between CKD status and the effect of beta-blockers on all-cause mortality were nonsignificant in each of the 5 post-hoc CKD subgroup analyses of larger trials, indicating that the treatment effect was similar in CKD patients and those without CKD. Data on cardiovascular mortality were reported from 4 trials (n = 3,384) with results that again favored beta-blockers (RR: 0.66, 95% CI: 0.49 to 0.89, p = 0.006) (Fig. 4), although moderate level heterogeneity was present (I-square = 64.2%, p = 0.045).

Only 1 trial included dialysis patients (40), and the overall results were not significantly changed by exclusion of this study for mortality (RR: 0.72, 95% CI: 0.64 to 0.81, p < 0.001; test for heterogeneity: I-square = 0%, p = 0.435), whereas the effects on cardiovascular mortality became more clearly beneficial and consistent (3,270 nondialysis patients; 3 trials; RR: 0.76, 95% CI: 0.64 to 0.90, p = 0.001; test for heterogeneity: I-square = 0%, p = 0.92).

The risk of sudden death was also reduced by beta-blockers (4 trials; RR: 0.70, 95% CI: 0.55 to 0.89, p = 0.004; test for heterogeneity: I-square = 0%, p = 0.491) (Online Fig. 1), whereas beta-blockers did not significantly affect the risk of all-cause hospitalization (2 trials; RR: 0.75, 95% CI: 0.52 to 1.08, p = 0.121; test for heterogeneity: I-square = 67.1%, p = 0.050). Summary statistics for hospitalization for worsening of heart failure are not reported due to the presence of high-level heterogeneity (4 trials; I-square = 82.5%, p = 0.003).

**NON–HEART FAILURE STUDIES.** There were substantial differences in the baseline eGFR and blood pressure target between the 2 non–heart failure studies (46,47). Due to the relatively larger sample size and number of mortality events, the AASK (African American Study of Kidney Disease and Hypertension) trial (46) dominated the pooled estimates with a weighting of 96.3%. Therefore, a quantitative meta-analysis is not reported. Data on cardiovascular mortality was only reported in 1 trial, so meta-analysis was not possible.

**Adverse effects.** **HEART FAILURE STUDIES.** There was inadequate reporting of rates of study medication discontinuation due to adverse events in 3 trials (43,44). In the remaining 3 trials, discontinuation of study medication in the beta-blocker arm was comparable to the control arm (3 trials RR: 1.17, 95% CI: 0.66 to 2.09, p = 0.585; I-square =
59.2%, \( p = 0.086 \) (Fig. 5) (40–42). Compared with placebo, treatment with beta-blockers was associated with increased risk of bradycardia (4 trials; RR: 4.92, 95% CI: 3.20 to 7.55, \( p < 0.001 \); I-square = 0%, \( p = 0.838 \)) and hypotension (4 trials; RR: 5.08, 95% CI: 3.48 to 7.41, \( p < 0.001 \); I-square = 0%, \( p = 0.941 \)) (Fig. 5) (40,41,44). The risk of hyperkalemia was similar in the 2 groups (3 trials; RR: 2.16, 95% CI: 0.12 to 37.92, \( p = 0.6 \); I-square = 68.2%, \( p = 0.076 \)) (Fig. 5) (40,44). Data on hyperglycemia was reported in 1 trial only, hence a meta-analysis was not possible.

**NON–HEART FAILURE STUDIES.** Data on study medication discontinuation due to adverse events (47) and hyperkalemia (46) was reported in 1 trial each, so meta-analysis not possible for these adverse events. Neither of the trials reported data on bradycardia, hypotension, and hyperglycemia.

**Discussion**

This meta-analysis has demonstrated a 28% and 34% relative reduction in all-cause and cardiovascular mortality, respectively, with beta-blocker therapy in patients with
heart failure and CKD. Compared with placebo, there was an increased risk of bradycardia and hypotension with beta-blocker therapy in patients with heart failure. Only 1 trial assessing major clinical outcomes was designed to include patients receiving dialysis. There is a paucity of data on the effect of beta-blockers on patient-level clinical outcomes in CKD patients without heart failure.

The excess burden of cardiovascular disease in patients with CKD contributes to their poor survival (6–8). This is likely partly due to traditional cardiovascular risk factors such as hypertension, older age, dyslipidemia, and diabetes, as these are highly prevalent in CKD patients (13,50). In addition, a combination of “nontraditional” risk factors including anemia, hyperphosphatemia, chronic inflammation, oxidative stress, volume overload, medial vascular calcification, and sympathetic nervous system overactivity have been identified in this patient population. These risk factors are also likely to contribute to elevated cardiovascular risk (25,51). Randomized controlled trials assessing standard cardiovascular therapies in CKD patients have often yielded disappointing results (52–54), possibly due to the multifactorial nature of cardiovascular disease in CKD.

Given the high prevalence of heart failure (31% to 40%), ischemic heart disease (33% to 39%), and arrhythmia (7% to 9%), it is critical to identify risk factors and develop targeted therapeutic strategies to improve outcomes in this patient population. The results of the CAPRICORN and COPERNICUS trials provide valuable insights into the effects of beta-blockers in CKD patients with heart failure, and these findings may have implications for the broader management of cardiovascular disease in this challenging patient group.
31%) in CKD patients (7,55), particular those requiring dialysis (8), it is possible that CKD patients may derive benefit from beta-blocker therapy that is similar to or perhaps greater than that observed in other populations (14,15). In this systematic review, data regarding nondialysis CKD patients was obtained exclusively from post hoc subgroup analyses of RCTs in patients with heart failure. Although these studies were not specifically designed to assess effects in people with CKD, the absence of an interaction suggests that the benefits for all-cause and cardiovascular mortality in nondialysis CKD patients are similar to those in people who do not have CKD. Given that patients with CKD have a higher frequency of cardiovascular events than patients with GFR >60 ml/min/1.73 m² do, the absolute risk reduction with beta-blocker therapy should be much greater in this group.

This systematic review also highlights the absence of specific evidence that beta-blockers reduce all-cause or cardiovascular mortality in the individuals with CKD who do not have heart failure, particularly those undergoing dialysis. Such individuals may still have ischemic heart disease or arrhythmias and thus may derive benefit from beta-blockers. However, in patients undergoing hemodialysis, the hypotensive side effects of beta-blockers may be exacerbated by marked fluctuations in extracellular fluid volume. Only 1 trial reported clinical outcomes in dialysis patients (40,49), and this included only 114 patients with symptomatic heart failure, contributing less than 15% of the weight for the mortality outcome. The small sample size and the lack of blinding during the second 12-month period of the study (when most events occurred) suggest that more studies are required.

**Study limitations.** The limitations of this systematic review include the relatively small number of eligible studies, the post hoc nature of analyses of the largest studies, the difficulties in defining “symptomatic” heart failure in patients with CKD, and the lack of systematic data on adverse effects. In this systematic review, data regarding nondialysis CKD patients was obtained exclusively from post hoc subgroup analyses of RCTs in patients with heart failure that defined CKD as an eGFR <60 ml/min/1.73 m². Because patients with advanced CKD were excluded from these 5 heart failure studies, the majority of participants in the CKD subgroups had relatively mild CKD. For example, 60% and 66% of participants from the CKD cohort of the CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) (43) and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) (42) studies, respectively, had an eGFR between 45 and 60 ml/min/1.73 m² at baseline. In the combined cohort of CAPRICORN (Carvedilol Post-Infarct Survival Controlled Evaluation) and COPERNICUS (Effect of Carvedilol on Survival in Severe Chronic Heart Failure) studies, only 8% of all CKD participants had GFR <30 ml/min/1.73 m² (44). Therefore, the application of these results to patients with very low levels of GFR (particularly <30 ml/min/1.73 m²) is limited by the smaller number of participants with such low GFR in these studies.

The definition of heart failure in terms of presence and severity of symptoms was not uniform across the studies and almost all studies defined patients as “symptomatic” based on the New York Heart Association functional classification of symptoms. Patients with CKD may report symptoms of heart failure, such as fatigue or dyspnea, even in the absence of heart failure. This was demonstrated in an analysis of 2,883 CKD patients without heart failure, in which 25% of the cohort had the modified Kansas City Cardiomyopathy Questionnaire score <75, a threshold suggestive of moderate burden of heart failure symptoms (56). However, as described in Table 1, all studies were uniformly composed of participants with low left ventricular ejection fraction (LVEF). Hence, the findings of this systematic review apply to patients with CKD and heart failure with decreased LVEF, but not to patients with heart failure and preserved LVEF.

**Conclusions**

This systematic review demonstrates that treatment with beta-blockers decreased all-cause and cardiovascular mortality in patients with CKD who have heart failure and low LVEF, suggesting these individuals will obtain similar or greater benefits than people with heart failure who do not have CKD. The widespread use of beta-blockers to reduce cardiovascular events and improve patient-level outcomes in patients with CKD who do not have heart failure or those with symptomatic heart failure and a normal LVEF cannot be recommended based on existing RCT evidence. The need for adequately powered prospective RCTs assessing the effects of beta-blockers in a broader population of individuals with advanced CKD are supported by the demonstrated effects in people with CKD and heart failure, as well as by the known cardiovascular pathophysiology that has been described in this patient population. Such trials should provide a clear demonstration of the benefits and risks associated with beta-blockers in patients with advanced CKD, particularly those receiving dialysis, and inform potential use of a treatment to reduce the burden of death and disability suffered by this patient population.

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**REFERENCES**


Key Words: beta-adrenergic antagonists • cardiovascular disease • chronic kidney disease • heart failure • meta-analysis.

APPENDIX

For the complete search strategy, please see the online version of this article.