

# Chronic Kidney Disease and the Risk for Cardiovascular Disease, Renal Replacement, and Death in the United States Medicare Population, 1998 to 1999

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Knowledge of the excess risk posed by specific cardiovascular syndromes could help in the development of strategies to reduce premature mortality among patients with chronic kidney disease (CKD). The rates of atherosclerotic vascular disease, congestive heart failure, renal replacement therapy, and death were compared in a 5% sample of the United States Medicare population in 1998 and 1999 ( $n = 1,091,201$ ). Patients were divided into the following groups: 1, no diabetes, no CKD (79.7%); 2, diabetes, no CKD (16.5%); 3, CKD, no diabetes (2.2%); and 4, both CKD and diabetes (1.6%). During the 2 yr of follow-up, the rates (per 100 patient-years) in the four groups were as follows: atherosclerotic vascular disease, 14.1, 25.3, 35.7, and 49.1; congestive heart failure, 8.6, 18.5, 30.7, and 52.3; renal replacement therapy, 0.04, 0.2, 1.6, and 3.4; and death, 5.5, 8.1, 17.7, and 19.9, respectively ( $P < 0.0001$ ). With use of Cox regression, the corresponding adjusted hazards ratios were as follows: atherosclerotic vascular disease, 1, 1.30, 1.16, and 1.41 ( $P < 0.0001$ ); congestive heart failure, 1, 1.44, 1.28, and 1.79 ( $P < 0.0001$ ); renal replacement therapy, 1, 2.52, 23.1, and 38.9 ( $P < 0.0001$ ); and death, 1, 1.21, 1.38, and 1.56 ( $P < 0.0001$ ). On a relative basis, patients with CKD were at a much greater risk for the least frequent study outcome, renal replacement therapy. On an absolute basis, however, the high death rates of patients with CKD may reflect accelerated rates of atherosclerotic vascular disease and congestive heart failure.

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Chronic kidney disease (CKD) has become a common condition in the general population (1). Aging of the general population and an ongoing epidemic of diabetes are probable contributory factors (2). Some (3–5) but not all (6) recent studies have shown that patients with CKD have higher-than-expected death rates, even after adjustment for adverse prognostic factors that co-occur with CKD, such as older age, diabetes, and previous cardiovascular disease. Other studies suggest that CKD may act as a risk multiplier in patients who are hospitalized with symptomatic manifestations of cardiovascular disease, including patients with myocardial infarction and those with congestive heart failure (7–18). Renal replacement therapy is orders of magnitude less prevalent than CKD (19). These different strands of evidence suggest that identifying patients with CKD may have an importance beyond the mere identification of patients who are at risk for progressing to ESRD (20). The hypothesis that the higher death risk associated with CKD reflects higher rates of atherosclerotic

vascular disease and congestive heart failure has clinical relevance. Kidney disease and cardiovascular disease both are approaching epidemic levels in the elderly. Both conditions seem to be lethally synergistic. Enumerating the degree by which kidney disease magnifies the risk for cardiovascular disease might inform screening and management strategies. For example, treating physicians might make greater efforts to identify and slow the progression of CKD and to treat modifiable risk factors such as obesity, lack of exercise, smoking, hyperlipidemia, and hypertension.

## Materials and Methods

The objectives of this study were to compare patients with and without CKD on the basis of (1) cross-sectional associations with diabetes, age, demographic cardiovascular disease, and other comorbid conditions; (2) incidence of atherosclerotic vascular disease; (3) incidence of congestive heart failure; (4) incidence of renal replacement therapy; and (5) overall survival rates.

## Design

Two phases were used. In the first phase, we identified Medicare patients who met the entry criteria (see the Patients section), which included survival from January 1, 1998, to December 31, 1999. Medicare claims during this 2-yr period were used to define patient characteristics, including age and the presence of CKD and/or diabetes on De-

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cember 31, 1999. The second phase, which extended from January 1, 2000, to December 31, 2001, was used to define the major study outcomes.

### Patients

We used the Medicare 5% Denominator File, a random sample based on health insurance claim numbers, to identify patients with the following characteristics: (1) age  $\geq 65$  yr on January 1, 1998; (2) residing in the 50 U.S. states, the District of Columbia, Puerto Rico, or the U.S. territories; (3) alive on December 31, 1999; (4) not receiving renal replacement therapy on December 31, 1999; and (5) continuously enrolled in both Medicare Part A and Part B from January 1, 1998, to December 31, 1999. Patients who were enrolled in a health maintenance organization and those with Medicare as secondary payer during this period were excluded.

Clinical conditions, with the exception of renal replacement therapy, were identified from Medicare claims according to a previously validated method for identifying diabetes (21). The *International Classification of Diseases, Ninth Revision, Clinical Modification* codes used to define each condition are shown in Appendix 1. Renal replacement therapy was identified by linking the Medicare 5% Denominator File to the United States Renal Data System database, which includes information on all patients who enter the renal replacement therapy program.

### Statistical Analyses

The baseline associations of the four groups defined by the presence or absence of kidney disease and diabetes, as of December 31, 1999, were compared using  $\chi^2$  analysis. In addition, the associations of CKD were examined using a logistic regression model in which diabetes was added to age, demographic variables, and clinical variables.

For each of the incident clinical outcomes, follow-up extended from January 1, 2000, until the earliest occurrence of the clinical event in question, renal replacement therapy, death, or December 31, 2001. We calculated event rates in each of the four groups defined by the presence or absence of kidney disease and diabetes. Population-attributable proportions for clinical events, according to the presence or absence of diabetes and/or CKD, were calculated as the product of (event rate in the exposed group – event rate in the nonexposed group)  $\times$  (proportion of the population with the exposure of interest)  $\div$  (overall population rate event rate). The association between CKD and incident clinical outcomes was examined using Cox regression models that adjusted for diabetes, age, demographic variables, and clinical variables. All analyses were performed using SAS/STAT, version 8.2 (SAS Institute, Inc., Cary, NC).

## Results

Table 1 shows the characteristics of the 1,091,201 study subjects as of December 31, 1999. The proportions with CKD (but not diabetes), with diabetes (but not CKD), and with both conditions were 2.2, 16.5, and 1.6%, respectively. Twenty-two percent of the study population had previous atherosclerotic vascular disease, and 13.8% had previous congestive heart failure. Using multivariate logistic regression, the following factors showed the largest cross-sectional associations ( $P < 0.0001$ ) with CKD, based on adjusted odds ratios (OR): days hospitalized in the preceding 2 yr (OR, 4.62 for  $\geq 20$  d), anemia (OR, 2.13), hypertension (OR, 2.10), diabetes (OR, 2.04), congestive heart failure (OR, 1.96), male gender (OR, 1.56), liver disease (OR, 1.51), cancer (OR, 1.44), atherosclerotic vascular disease (OR, 1.42), and older age (OR, 1.10 for age  $\geq 80$  yr).

The defining cause of CKD was glomerulonephritis in 59.6%, hydronephrosis in 9.7%, diabetic nephropathy in 7.6%, hypertensive renal disease in 6.6%, kidney malignancy in 5.2%, renovascular disease in 4.9%, and other in 6.4%. Epoetin- $\alpha$  was used by 0.45% of the population studied (0.29% of non-CKD, nondiabetic subjects; 0.39% of non-CKD, diabetic subjects; 3.81% of CKD, nondiabetic subjects; and 4.33% of CKD, diabetic subjects). The corresponding figures for general urinalysis were 44.36, 41.86, 52.52, 61.60, and 44.36%; for urinalysis for microalbuminuria were 1.69, 0.25, 7.90, 0.85, and 10.20%; and for urinalysis for protein were 10.78, 9.35, 14.68, 21.17, and 10.78%.

Table 2 shows that the rates of the major study outcomes (*i.e.*, atherosclerotic vascular disease, congestive heart failure, renal replacement therapy, and death) were 16.5, 10.8, 0.14, and 6.4 per 100 patient-years, respectively. Patients with CKD and diabetes had higher event rates than patients without these conditions ( $P < 0.0001$ ). In nondiabetic patients, on an absolute basis, the largest discrepancy between those with and those without CKD was for congestive heart failure, with a difference in event rates of 22.1 per 100 patient-years, followed by atherosclerotic vascular disease (21.6 per 100 patient-years), death (12.2 per 100 patient-years), and renal replacement therapy (1.56 per 100 patient-years). Similar patterns were present among patients with diabetes, in whom the differences in event rates were 33.8 per 100 patient-years for congestive heart failure, 23.8 per 100 patient-years for atherosclerotic vascular disease, 11.8 per 100 patient-years for death, and 3.2 per 100 patient-years for renal replacement therapy. Figure 1 shows the corresponding population-attributable proportions for congestive heart failure, atherosclerotic vascular disease, renal replacement therapy, and death.

Table 3 shows adjusted hazards ratios for incident events in 2000 to 2001. CKD and diabetes were associated with each outcome. For atherosclerotic vascular disease and congestive heart failure, the following monotonic risk pattern was present: no CKD, no diabetes  $<$  CKD alone  $<$  diabetes alone  $<$  both CKD and diabetes. In contrast, for renal replacement therapy and death, the risk pattern was no CKD, no diabetes  $<$  diabetes alone  $<$  CKD alone  $<$  both CKD and diabetes. Adding epoetin- $\alpha$ , general urinalysis, urinalysis for microalbuminuria, and urinalysis for protein as covariates had negligible effects on the hazards ratios reported in Table 3.

## Discussion

We found, on a relative basis, that the risk gradient associated with CKD was much greater for renal replacement therapy than it was for those associated with congestive heart failure and atherosclerotic vascular disease. However, atherosclerotic events and congestive heart failure were much more frequent in the study population than was renal replacement therapy. On an absolute basis, the high death rates among patients with CKD may reflect accelerated rates of atherosclerotic vascular disease and congestive heart failure.

It is not surprising that patients with CKD should be at a higher risk for ESRD than those without CKD. Also, the association between CKD and death that we observed has recently been observed by others (2–5). Recent studies in a general-

Table 1. Baseline patient characteristics on December 31, 1999<sup>a</sup>

| Characteristic                 | Patients by Diabetes/CKD Group                   |   |   |   |   | <i>P</i> <sup>b</sup> | CKD                      |                       |
|--------------------------------|--|---|---|---|---|-----------------------|--------------------------|-----------------------|
|                                | All Patients<br>( <i>n</i> = 1,091,201;<br>100%) | Non-Diabetes/<br>Non-CKD<br>( <i>n</i> = 869,902;<br>79.7%) | Diabetes/<br>Non-CKD<br>( <i>n</i> = 179,777;<br>16.5%) | Non-Diabetes/<br>CKD<br>( <i>n</i> = 23,573;<br>2.2%) | Diabetes/<br>CKD<br>( <i>n</i> = 17,949;<br>1.6%) |                       | OR (95% CI) <sup>c</sup> | <i>P</i> <sup>c</sup> |
| Diabetes                       | 18.1%  | 0.0%  | 100%  | 0.0%  | 100%  |                       | 2.04 (2.00–2.09)         | <0.0001               |
| Age on December 31, 1999 (yr)  |  |   |   |   |   | <0.0001               |                          |                       |
| 67–69                          | 16.0%  | 16.4%   | 15.5%   | 9.0%  | 12.7%   |                       | 1                        |                       |
| 70–74                          | 27.8%  | 27.8%   | 28.8%   | 20.7%   | 26.0%   |                       | 1.05 (1.01–1.09)         | 0.0078                |
| 75–79                          | 24.5%  | 24.2%   | 26.1%   | 23.5%   | 27.5%   |                       | 1.08 (1.04–1.12)         | <0.0001               |
| ≥80                            | 31.6%  | 31.6%   | 29.6%   | 46.7%   | 33.8%   |                       | 1.10 (1.06–1.14)         | <0.0001               |
| Gender                         |  |   |   |   |   | <0.0001               |                          |                       |
| male                           | 39.2%  | 38.5%   | 40.7%   | 48.5%   | 46.5%   |                       | 1.56 (1.53–1.59)         | <0.0001               |
| female                         | 60.8%  | 61.5%   | 59.3%   | 51.5%   | 53.5%   |                       | 1                        |                       |
| Race                           |  |   |   |   |   | <0.0001               |                          |                       |
| white                          | 89.0%  | 90.4%   | 83.5%   | 86.9%   | 79.3%   |                       | 1                        |                       |
| black                          | 7.1%   | 6.2%  | 10.8%   | 9.8%  | 13.9%   |                       | 1.40 (1.35–1.44)         | <0.0001               |
| other                          | 3.9%   | 3.4%  | 5.7%  | 3.3%  | 6.8%  |                       | 1.24 (1.18–1.30)         | <0.0001               |
| Renal disease                  |  |   |   |   |   |                       |                          |                       |
| glomerulonephritis             |  |   |   | 60.2%   | 58.7%   |                       |                          |                       |
| diabetes                       |  |   |   | 0.0%  | 17.6%   |                       |                          |                       |
| hypertension                   |  |   |   | 8.1%  | 8.5%  |                       |                          |                       |
| renovascular                   |  |   |   | 5.9%  | 3.6%  |                       |                          |                       |
| hydronephrosis                 |  |   |   | 12.7%   | 5.8%  |                       |                          |                       |
| urological                     |  |   |   | 7.3%  | 2.9%  |                       |                          |                       |
| malignancy                     |  |   |   |   |   |                       |                          |                       |
| other                          |  |   |   | 5.9%  | 2.9%  |                       |                          |                       |
| Total hospital days, 1998–1999 |  |   |   |   |   | <0.0001               |                          |                       |
| none                           | 69.0%  | 73.3%   | 58.4%   | 27.3%   | 23.9%   |                       | 1                        |                       |
| 1–4                            | 14.2%  | 13.5%   | 17.2%   | 18.8%   | 15.8%   |                       | 1.90 (1.83–1.96)         | <0.0001               |
| 5–9                            | 6.1%   | 5.3%  | 8.3%  | 13.7%   | 11.9%   |                       | 2.52 (2.43–2.61)         | <0.0001               |
| 10–19                          | 6.0%   | 4.8%  | 8.8%  | 18.8%   | 18.6%   |                       | 3.22 (3.11–3.34)         | <0.0001               |
| ≥20                            | 4.7%   | 3.1%  | 7.3%  | 21.4%   | 29.8%   |                       | 4.62 (4.45–4.79)         | <0.0001               |
| Comorbidity                    |  |   |   |   |   |                       |                          |                       |
| AMI                            | 2.5%   | 1.8%  | 4.2%  | 8.4%  | 12.1%   | <0.0001               | ND                       | ND                    |
| CVA/TIA                        | 12.3%  | 10.3%   | 18.2%   | 25.6%   | 31.8%   | <0.0001               | ND                       | ND                    |
| PVD                            | 12.0%  | 9.6%  | 18.0%   | 32.6%   | 38.6%   | <0.0001               | ND                       | ND                    |
| ASVD <sup>d</sup>              | 21.8%  | 18.2%   | 32.0%   | 48.1%   | 57.3%   | <0.0001               | 1.42 (1.38–1.45)         | <0.0001               |
| anemia                         | 16.7%  | 14.1%   | 21.9%   | 47.0%   | 51.7%   | <0.0001               | 2.13 (2.08–2.18)         | <0.0001               |
| CHF                            | 13.8%  | 10.5%   | 22.4%   | 39.9%   | 54.1%   | <0.0001               | 1.96 (1.91–2.01)         | <0.0001               |
| cancer                         | 19.2%  | 18.5%   | 19.7%   | 36.2%   | 26.3%   | <0.0001               | 1.44 (1.41–1.48)         | <0.0001               |
| COPD                           | 15.3%  | 14.1%   | 17.7%   | 29.7%   | 30.8%   | <0.0001               | 1.01 (0.98–1.03)         | 0.4532                |
| gastrointestinal bleeding      | 6.1%   | 5.4%  | 7.5%  | 16.1%   | 18.3%   | <0.0001               | 1.06 (1.03–1.10)         | <0.0001               |
| liver disease                  | 0.8%   | 0.6%  | 1.5%  | 2.0%  | 3.6%  | <0.0001               | 1.51 (1.41–1.62)         | <0.0001               |
| hypertension                   | 54.2%  | 48.8%   | 73.9%   | 78.6%   | 88.9%   | <0.0001               | 2.10 (2.04–2.16)         | <0.0001               |
| Care indicators                |  |   |   |   |   |                       |                          |                       |
| epoetin use                    | 0.5%   | 0.3%  | 0.4%  | 3.8%  | 4.3%  | <0.0001               |                          |                       |
| general urinalysis             | 44.4%  | 41.9%   | 52.5%   | 61.2%   | 61.6%   | <0.0001               |                          |                       |
| microalbuminuria test          | 1.7%   | 0.3%  | 7.9%  | 0.9%  | 10.2%   | <0.0001               |                          |                       |
| urinalysis for protein         | 10.8%  | 9.4%  | 14.7%   | 21.2%   | 27.1%   | <0.0001               |                          |                       |

<sup>a</sup>Percentages indicate proportions within columns; italicized percentages within column headings indicate proportions of all patients. AMI, acute myocardial infarction; ASVD, atherosclerotic vascular disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ND, not determined; OR, odds ratio; PVD, peripheral vascular disease; TIA, transient ischemic attack.

<sup>b</sup>Using the  $\chi^2$  test.

<sup>c</sup>Using logistic regression with the presence (coded as 1) or absence (coded as 0) of CKD as the dependent variable and diabetes, age, gender, race, hospital days in 1998 to 1999, ASVD, anemia, CHF, cancer, gastrointestinal bleeding, liver disease, and hypertension as exploratory variables. The reference categories were absence of diabetes, age 67 yo 69 yr, female gender, white race, no days in hospital in 1998 to 1999, and absence of comorbid conditions.

<sup>d</sup>ASVD was defined as the presence of AMI, CVA/TIA, or PVD.

Table 2. Incident event rates in 2000 to 2001<sup>a</sup>

| Group                | CHF         | AMI        | CVA/TIA     | PVD         | ASVD <sup>b</sup> | RRT          | Death       |
|----------------------|-------------|------------|-------------|-------------|-------------------|--------------|-------------|
| All patients         | 10.8 (0.02) | 1.9 (0.01) | 8.8 (0.02)  | 8.3 (0.02)  | 16.5 (0.03)       | 0.14 (0.003) | 6.4 (0.02)  |
| Non-diabetes/non-CKD | 8.6 (0.02)  | 1.6 (0.01) | 7.6 (0.02)  | 6.9 (0.02)  | 14.1 (0.03)       | 0.04 (0.002) | 5.5 (0.02)  |
| Diabetes/non-CKD     | 18.5 (0.08) | 3.2 (0.03) | 13.1 (0.07) | 12.8 (0.07) | 25.3 (0.10)       | 0.2 (0.01)   | 8.1 (0.05)  |
| Non-diabetes/CKD     | 30.7 (0.32) | 3.9 (0.10) | 16.6 (0.22) | 19.9 (0.25) | 35.7 (0.36)       | 1.6 (0.06)   | 17.7 (0.21) |
| Diabetes/CKD         | 52.3 (0.53) | 6.9 (0.16) | 22.0 (0.31) | 26.6 (0.35) | 49.1 (0.51)       | 3.4 (0.11)   | 19.9 (0.27) |

<sup>a</sup>Rates are reported per 100 patient-years, with SE in parentheses. RRT, renal replacement therapy.

<sup>b</sup>ASVD was defined as first occurrence of AMI, CVA/TIA, or PVD.

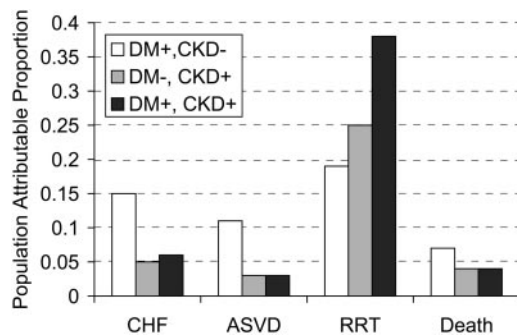


Figure 1. Population-attributable proportions (according to the presence of diabetes and/or chronic kidney disease [CKD]) for congestive heart failure, atherosclerotic vascular disease, renal replacement therapy, and death. Population-attributable proportions in the three exposure groups were calculated as (event rate in the exposed group – event rates in the group with neither diabetes nor CKD) × (proportion of the population with the exposure of interest) ÷ (overall population event rate). ASVD, atherosclerotic vascular disease; CHF, congestive heart failure, DM, diabetes mellitus; RRT, renal replacement therapy.

population setting have suggested that mild to moderate CKD is associated with future cardiovascular events. The Cardiovascular Health Study was a prospective population-based study of subjects aged  $\geq 65$  yr, with an average follow-up of 7.3 yr. Renal insufficiency, defined as a serum creatinine value  $>1.5$  mg/dl in men and  $>1.3$  mg/dl in women, was present in 11.2% of participants. Subjects with renal insufficiency were more likely to develop cardiovascular disease, congestive heart failure, and symptomatic peripheral vascular disease, as well as to die; these associations were not eliminated by adjusting for traditional cardiovascular risk factors (3). Similarly, the Atherosclerosis Risk in Communities study, a prospective cohort study of subjects aged 45 to 64 yr, reported that a declining GFR was independently associated with the development of atherosclerotic cardiovascular disease (22). These findings are consistent with animal models suggesting that the metabolic internal milieu of CKD is both cardiotoxic and vasculotoxic (23,24).

Our study has several limitations. It was retrospective and used administrative claims to define the study population and the outcomes of interest. In particular, the assessment of CKD was not based on systematic estimates of kidney function but rather on qualitative clinical events. It is possible, therefore, that

these “index” events account for some of the associations in this study. The proportion of the Medicare population with a diagnosis, by claims, of CKD was similar to the proportion of the general population with an estimated GFR of  $<60$  ml/min per  $1.73$  m<sup>2</sup>; we suspect that most of the patients whom we studied fell into stage 3 (GFR, 30 to 59 ml/min per  $1.73$  m<sup>2</sup>), 4 (GFR, 15 to 29 ml/min per  $1.73$  m<sup>2</sup>), or 5 (kidney failure) of CKD (19). Similarly, characterization of comorbid conditions was heavily dependent on clinical events rather than systematic sampling. Validation of each of the variables studied here is clearly desirable. This is not an insignificant undertaking, however, as claims-based studies do not lend themselves easily to rigorous validation: In essence, a large-scale, national prospective study is required. Misclassification, whereby patients who, in reality, have CKD are considered as normal, and *vice versa*, would tend to bias toward the null. Thus, the CKD-associated risk gradients presented in this study may underestimate the true risk gradients associated with CKD. Finally, we examined a subset of patients, those who survived for 2 yr (January 1, 1998, to December 31, 1999); this was necessary to establish meaningful patient profiles. Similarly, this study included only Medicare enrollees, and its findings cannot be generalized to other populations.

We believe that the study has strengths. The sample size is large; therefore, the risk estimates have relatively tight confidence intervals. Comorbidity adjustment was extensive, and several events, based on clinical reality, were examined concurrently. We believe that this study has important implications. On an absolute basis, in patients with CKD, the risks for atherosclerotic vascular disease and congestive heart failure seem to be much greater than the risk for renal replacement therapy. Our findings suggest that screening strategies and therapeutic management should be tailored as much toward the prevention of cardiovascular disease as toward the prevention of ESRD.

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Table 3. Adjusted hazards ratios (with 95% CI) for incident events in 2000 to 2001<sup>a</sup>

|                                   | ASVD             | P       | CHF              | P       | RRT              | P       | Death            | P       |
|-----------------------------------|------------------|---------|------------------|---------|------------------|---------|------------------|---------|
| Non-diabetes/non-CKD              | 1 (reference)    |         | 1                |         | 1                |         | 1                |         |
| Diabetes/non-CKD                  | 1.30 (1.29-1.31) | <0.0001 | 1.44 (1.42-1.45) | <0.0001 | 2.52 (2.24-2.83) | <0.0001 | 1.21 (1.19-1.22) | <0.0001 |
| Non-diabetes/CKD                  | 1.16 (1.14-1.19) | <0.0001 | 1.28 (1.25-1.31) | <0.0001 | 23.1 (20.6-26.0) | <0.0001 | 1.38 (1.34-1.41) | <0.0001 |
| Diabetes/CKD                      | 1.41 (1.37-1.44) | <0.0001 | 1.79 (1.75-1.83) | <0.0001 | 38.9 (34.7-43.6) | <0.0001 | 1.56 (1.52-1.61) | <0.0001 |
| Age on December 31, 1999 (yr)     |                  |         |                  |         |                  |         |                  |         |
| 67-69                             | 1                |         | 1                |         | 1                |         | 1                |         |
| 70-74                             | 1.23 (1.22-1.25) | <0.0001 | 1.23 (1.20-1.25) | <0.0001 | 0.91 (0.81-1.02) | 0.0901  | 1.30 (1.27-1.34) | <0.0001 |
| 75-79                             | 1.53 (1.51-1.55) | <0.0001 | 1.56 (1.53-1.59) | <0.0001 | 0.80 (0.71-0.90) | 0.0002  | 1.87 (1.83-1.92) | <0.0001 |
| ≥80                               | 2.01 (1.99-2.04) | <0.0001 | 2.31 (2.27-2.35) | <0.0001 | 0.60 (0.53-0.68) | <0.0001 | 4.00 (3.91-4.10) | <0.0001 |
| Gender                            |                  |         |                  |         |                  |         |                  |         |
| male                              | 1.10 (1.09-1.11) | <0.0001 | 1.12 (1.11-1.13) | <0.0001 | 1.47 (1.36-1.59) | <0.0001 | 1.22 (1.21-1.24) | <0.0001 |
| female                            | 1                |         | 1                |         | 1                |         | 1                |         |
| Race                              |                  |         |                  |         |                  |         |                  |         |
| white                             | 1                |         | 1                |         | 1                |         | 1                |         |
| black                             | 1.06 (1.05-1.07) | <0.0001 | 1.05 (1.04-1.07) | <0.0001 | 2.09 (1.90-2.29) | <0.0001 | 1.10 (1.08-1.13) | <0.0001 |
| other                             | 0.89 (0.87-0.91) | <0.0001 | 0.89 (0.87-0.91) | <0.0001 | 1.28 (1.10-1.51) | 0.0021  | 0.88 (0.85-0.91) | <0.0001 |
| Total hospital days, 1998 to 1999 |                  |         |                  |         |                  |         |                  |         |
| none                              | 1                |         | 1                |         | 1                |         | 1                |         |
| 1-4                               | 1.04 (1.03-1.05) | <0.0001 | 1.15 (1.14-1.17) | <0.0001 | 0.92 (0.82-1.03) | 0.1593  | 1.22 (1.20-1.24) | <0.0001 |
| 5-9                               | 1.02 (1.01-1.03) | 0.0009  | 1.12 (1.11-1.14) | <0.0001 | 0.81 (0.71-0.91) | 0.0006  | 1.47 (1.44-1.50) | <0.0001 |
| 10-19                             | 1.03 (1.02-1.04) | <0.0001 | 1.15 (1.13-1.17) | <0.0001 | 0.74 (0.64-0.84) | <0.0001 | 1.67 (1.64-1.71) | <0.0001 |
| ≥20                               | 1.21 (1.19-1.23) | <0.0001 | 1.21 (1.19-1.23) | <0.0001 | 0.52 (0.45-0.60) | <0.0001 | 2.01 (1.97-2.06) | <0.0001 |
| Comorbidity                       |                  |         |                  |         |                  |         |                  |         |
| ASVD                              | 4.89 (4.85-4.93) | <0.0001 | 1.24 (1.23-1.25) | <0.0001 | 1.03 (0.95-1.12) | 0.4819  | 1.46 (1.44-1.48) | <0.0001 |
| anemia                            | 1.09 (1.08-1.10) | <0.0001 | 1.11 (1.10-1.12) | <0.0001 | 2.42 (2.22-2.64) | <0.0001 | 1.29 (1.28-1.31) | <0.0001 |
| CHF                               | 1.18 (1.17-1.19) | <0.0001 | 7.99 (7.91-8.08) | <0.0001 | 1.85 (1.69-2.02) | <0.0001 | 1.79 (1.77-1.82) | <0.0001 |
| cancer                            | 0.99 (0.98-1.00) | 0.0103  | 0.97 (0.96-0.98) | <0.0001 | 0.99 (0.91-1.08) | 0.8202  | 1.27 (1.25-1.28) | <0.0001 |
| COPD                              | 1.14 (1.13-1.15) | <0.0001 | 1.37 (1.35-1.38) | <0.0001 | 0.80 (0.73-0.88) | <0.0001 | 1.41 (1.39-1.43) | <0.0001 |
| gastrointestinal bleeding         | 1.06 (1.04-1.07) | <0.0001 | 1.04 (1.02-1.06) | <0.0001 | 0.94 (0.84-1.06) | 0.2949  | 1.03 (1.01-1.05) | 0.0004  |
| liver disease                     | 1.03 (1.00-1.07) | 0.0623  | 1.10 (1.06-1.14) | <0.0001 | 0.55 (0.39-0.76) | 0.0003  | 1.40 (1.34-1.46) | <0.0001 |
| hypertension                      | 1.22 (1.21-1.23) | <0.0001 | 1.20 (1.18-1.21) | <0.0001 | 1.84 (1.65-2.05) | <0.0001 | 0.78 (0.77-0.79) | <0.0001 |

<sup>a</sup>Using Cox regression. The exploratory variables were diabetes/CKD group, age, gender, race, hospital days in 1998 to 1999, ASVD, anemia, CHF, cancer, gastrointestinal bleeding, liver disease, and hypertension. The reference categories were absence of diabetes and CKD, age 67 to 69 yr, female gender, white race, no days in hospital in 1998 to 1999, and absence of comorbid conditions.

## Appendix 1. ICD-9-CM codes used to identify clinical conditions

| Condition                             | ICD-9-CM Diagnostic Codes   | ICD-9-CM V Code |
|---------------------------------------|---|-----------------|
| Chronic kidney disease                | 016.0, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403.X1, 404.X2, 404.X3, 440.1, 442.1, 447.3, 572.4, 580-588, 591, 642.1, 646.2, 753.12-753.17, 753.19, 753.2, 794.4 |                 |
| Diabetes                              | 250, 357.2, 362.0X, 366.41  |                 |
| Acute myocardial infarction           | 410, 410.X, 410.X0, 410.X1  |                 |
| Cerebrovascular accident/TIA          | 430-438   |                 |
| Peripheral vascular disease           | 440-444, 447, 557   |                 |
| Anemia                                | 280-285   |                 |
| Congestive heart failure              | 398.91, 425, 428, 402.X1, 404.X1, 404.X3  |                 |
| Cancer                                | 140-208, 230-234  | V10             |
| Chronic obstructive pulmonary disease | 491-494, 496, 510   |                 |
| Gastrointestinal bleeding             | 456.0-456.2, 530.7, 531-534, 569.84, 569.85, 578  |                 |
| Liver disease                         | 570, 571, 572.1, 572.4, 573.1-573.3   | V42.7           |
| Hypertension                          | 362.11, 401.X-405.X, 437.2  |                 |

ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; TIA, transient ischemic attack.

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