Chapter Five
Morbidity & mortality

The age as it flies glides secretly and deceives one and another; nothing is more fleeting than the years, but he who sows virtue reaps honor.

Leonardo da Vinci
Assessing morbidity in patients with chronic kidney disease (CKD) requires longitudinal data from a defined CKD population, with relatively complete information on all-cause and cause-specific hospitalization. Such data are rarely available on a random sample of the U.S. population, since it is very difficult to track patients across multiple insurers. Health plan datasets, however, can capture information well, particularly over a one-year period, and they provide a unique opportunity for analysis. In this chapter we use data from three insurers which represent large populations. Data from the Medicare system are very helpful, since the system covers 95 percent of individuals age 65 and older. We also examine data from the Thomson Rueters MarketScan dataset and the Ingenix i3 LabRx dataset, both from large employer group health plans (EGHPs). MarketScan data cover health plan expenditures for employers that are approximately 80 percent self-insured, compared to just 20 percent in the Ingenix i3 data. For each of these datasets we define CKD during a one-year entry period, noting hospitalizations and services in the one-year follow-up period. Increasing recognition of the CKD population can create biases in the data, in that patients who are diagnosed earlier in the course of their disease may have a lower disease burden. To address these potential biases we have added information on comorbidity and severity of disease. On the next page, for example, we examine hospitalizations in Medicare and MarketScan patients with and without CKD, showing both unadjusted and adjusted event rates. Unadjusted hospitalization rates in the CKD population are 3–5 times those of non-CKD patients. Once adjustments have been added for gender, prior hospitalizations, and comorbidity, however, hospitalization rates for CKD patients are approximately 1.5 times higher. Rates are greatest for Medicare patients and lower for younger patients with EGHP coverage. We next illustrate predictors of hospitalization over three time periods, noting that many predictors have similar hazard ratios in 2003, 2005, and 2007. Hospitalization rates for patients carrying the 585 ICD-9-CM diagnosis codes for CKD illustrate the graded effect of CKD stage. Trends in hospitalization rates — again adjusted for gender, prior hospitalization, and comorbidity — show a downward trend for both CKD and non-CKD patients. Interestingly, the reduction in rates over the last 12 years has been greatest for the CKD population. And not surprisingly, rates of cardiovascular hospitalization are greater for CKD patients, particularly in more advanced stages of the disease. Secondary to multiple defects in the ability to kill bacteria, infectious complications are more frequent in the CKD and dialysis populations. Adjusted rates of hospitalization for infection, for example, are 50–90 percent higher among Medicare and EGHP patients with CKD than in those without recognized kidney disease. Reductions in hospitalizations for pneumonia, however, are greater in CKD patients. Interestingly, hospitalizations secondary to bacteremia/sepsis show cyclical trends in both the CKD and non-CKD populations. The source of this pattern is unknown, but may reflect changes in the virulence...
of influenza over time. Rates of hospitalization for urinary tract infection have been relatively stable over time. We next compare mortality in the CKD and non-CKD populations, providing data on adjusted hazards of death, and illustrating the impact of comorbidity and severity of disease adjustments on absolute hazard ratios. With the non-CKD population as the reference, and adjusting for age, gender, race, and comorbidity, CKD is shown to significantly interact with diabetes and cardiovascular disease, approximately doubling the risk of mortality. In a similar way as for hospitalization, CKD is therefore a risk multiplier for mortality. The decline in mortality rates since 1995 partially reflects increased recognition of CKD, as illustrated by the increasing percentage of patients carrying the diagnosis; it may also show classification bias rather than a real reduction. Adjustments over time appear to mitigate some of these issues in recognition bias by addressing comorbidity and severity of disease. This year we have added information on cerebrovascular disease complications, events, and mortality in CKD patients and in those transitioning to ESRD. Rates of stroke generally increase with age and with CKD stage. There is also a striking increase in these rates during the two months prior to and following initiation of ESRD therapy. This period is associated with a three-fold increase in stroke rates, contributing to mortality early in the first year of dialysis — an issue that has received considerable attention, and is addressed in Chapter One of Volume Two.

**Figure 5.1**: see page 145 for analytical methods. Point prevalent Medicare (age 66 & older) & MarketScan (age 50–64) patients.
All HTN CVD COPD Admissions per 1,000 patient years

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2005</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>CI</td>
<td>RR</td>
</tr>
<tr>
<td>66–69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–74</td>
<td>1.15</td>
<td>1.139–1.169</td>
<td>1.18</td>
</tr>
<tr>
<td>75–84</td>
<td>1.45</td>
<td>1.434–1.468</td>
<td>1.48</td>
</tr>
<tr>
<td>85+</td>
<td>2.00</td>
<td>1.975–2.027</td>
<td>2.03</td>
</tr>
</tbody>
</table>

Table 5.4: Predictors of hospitalization in Medicare patients age 66 & older, by age, gender, race, at-risk group, & comorbidity

Predictors of hospitalization in Medicare patients age 66 & older:

- Hypertension
- Liver disease
- GI disease
- Cancer
- COPD
- Anemia

Predictors of hospitalization in Medicare patients age 66 & older, by CKD stage & comorbidity, 2007

Unadjusted & adjusted all-cause hospitalization rates in Medicare patients age 66 & older, by CKD stage & comorbidity, 2007

Overall hospitalization rates (adjusted for gender and severity of disease measures) for Medicare CKD patients are 1.5 times greater than for their younger MarketScan and Ingenix i3 counterparts with CKD, at 490 per 1,000 patient years compared to 326–329. Differences in hospitalization for infection are even greater, with admission rates in Medicare patients 1.8–2.0 times higher. Since 1995, rates of hospitalization for cardiovascular disease have fallen nearly 37 percent in the Medicare CKD population; in the years with available data, the MarketScan and Ingenix i3 CKD populations have seen declines of 18.1 and 17.7 percent. Rates of infectious hospitalization, however, have fallen just 12.3 percent since 1995 for Medicare patients, and since 2004 have increased 6.4 percent among Ingenix i3 patients. Figures 5.3–6; see page 145 for analytical methods. Point prevalent Medicare (age 66 & older) & MarketScan & Ingenix i3 (age 50–64) patients.
Adjusted all-cause hospitalization rates, by dataset & CKD status

Medicare (age 66+)

MarketScan (age 50-64)

Ingenix i3 (age 50-64)

Adjusted hospitalization rates for cardiovascular disease, by dataset & CKD status

Medicare (age 66+)

MarketScan (age 50-64)

Ingenix i3 (age 50-64)

Adjusted hospitalization rates for infection, by dataset & CKD status

Medicare (age 66+)

MarketScan (age 50-64)

Ingenix i3 (age 50-64)

Adjusted hospitalization rates for other causes, by dataset & CKD status

Medicare (age 66+)

MarketScan (age 50-64)

Ingenix i3 (age 50-64)
In 2007, adjusted hospitalization admissions for pneumonia among Medicare CKD patients age 66 and older reached 46.2 per 1,000 patient years nationwide, averaging 69.4 in the upper quintile. Overall admission rates for bacteremia/septicemia and urinary tract infections averaged 37.9 and 29.2, respectively, and in the upper quintile were 47.9 and 48.4 per 1,000 patient years. (Figures 5.7–9; see page 146 for analytical methods. Point prevalent Medicare CKD patients age 66 & older.

In the Medicare CKD population age 66 and older, hospitalization rates for pneumonia (adjusted for prior hospitalizations and measures of disease severity) are now 33.4 percent lower than in 1995. Rates of hospitalization for bacteremia/septicemia, in contrast, fell at the end of the last decade, but have since increased to 18.1 admissions per 1,000 patient years in 2007—a level 11.5 percent greater than in 1995. The number of admissions for urinary tract infections has remained relatively stable. (Figures 5.10–12; see page 146 for analytical methods. Point prevalent Medicare patients age 66 & older.
The overall adjusted rate of hospitalization for pneumonia among MarketScan CKD patients age 50–64 has fallen 49 percent since 2002, to 7.8 admissions per 1,000 patient years — 67 percent lower than the rate of 23.9 found in their older Medicare counterparts. The rate of hospitalization for bacteremia/septicemia in the MarketScan population, in contrast, has increased nearly 83 percent in the same period, reaching 9.3 admissions per 1,000 patient years; the rate among Medicare patients is nearly twice as high, at 18.2. Figures 5.13–15; see page 146 for analytical methods. Point prevalent MarketScan patients age 50–64.

In the Ingenix i3 CKD population (age 50–64), the adjusted rate of hospitalization for pneumonia in 2007 was slightly higher than among MarketScan patients, at 9.1 compared to 7.8 admissions per 1,000 patient years at risk. The admission rate for bacteremia/septicemia, however, was lower for Ingenix i3 patients, at 7.3 compared to 9.3 per 1,000 patient years in the MarketScan population. Rates of admission for urinary tract infection are comparable in the two populations, at 5.6 and 5.1, respectively. Figures 5.16–18; see page 146 for analytical methods. Point prevalent Ingenix i3 patients age 50–64.
These figures show mortality rates, since 1995, among Medicare patients age 66 and older, both unadjusted and adjusted for age (5.20–21) race, gender, hospitalization, and comorbidity. Unadjusted rates show what seem to be significant declines in mortality in the CKD population, with an overall decrease of 33 percent, and up to 48 percent in those age 70–74. When rates are adjusted for factors which address patient complexity, however, they begin to flatten out, implying that decreasing comorbidity and severity of disease in the patient population may explain part of the decline in mortality. More complete models, containing patient information which is not currently available in the claims data, may make these rates flatten even more. (Figures 5.19–21; see page 146 for analytical methods. Point prevalent Medicare patients age 66 & older.)
Relative risks in 2003, 2005, and 2007 show that age is a strong predictor of mortality, and show similar effects over time of age on the risk of death. In patients age 85 and older, the risk of death is more than six times higher than in patients age 66–69. For 2007 patients, the risk is 13 percent higher in males than in females, and 15 percent greater in African Americans compared to whites. The combined effects of CKD, diabetes, and cardiovascular disease (CVD) on the risk of death have declined since 2003, yet risks remain 3–4 times higher than those found in individuals without these conditions. Greater comorbidity increases the risk of death, and, compared to that of CVD, the presence of CKD appears to confer a similar risk for mortality.

Increasing comorbidity combinations of CKD, diabetes, and cardiovascular disease (CVD) confer increased risks of death. The risk has decreased since 2003 in individuals with a higher disease burden, yet remains two to three times higher in those with the most disease compared to those with no CKD, diabetes, or CVD.

**Table 5.2:** Relative risk of death in Medicare patients age 66 & older, by at-risk group.

<table>
<thead>
<tr>
<th>Condition</th>
<th>2003 RR (CI)</th>
<th>2005 RR (CI)</th>
<th>2007 RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CKD, DM, or CVD</td>
<td>reference</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>CKD (NDM, non-CVD)</td>
<td>1.99 (1.83 - 2.17)</td>
<td>1.60 (1.47 - 1.74)</td>
<td>1.72 (1.60 - 1.85)</td>
</tr>
<tr>
<td>DM (non-CKD, non-CVD)</td>
<td>1.23 (1.19 - 1.28)</td>
<td>1.22 (1.18 - 1.27)</td>
<td>1.12 (1.08 - 1.16)</td>
</tr>
<tr>
<td>CVD (non-CKD, non-DM)</td>
<td>1.84 (1.80 - 1.88)</td>
<td>1.81 (1.78 - 1.85)</td>
<td>1.80 (1.76 - 1.83)</td>
</tr>
<tr>
<td>CKD+DM</td>
<td>2.10 (1.86 - 2.37)</td>
<td>2.05 (1.84 - 2.28)</td>
<td>1.80 (1.63 - 1.98)</td>
</tr>
<tr>
<td>CKD+CVD</td>
<td>3.10 (2.98 - 3.22)</td>
<td>2.85 (2.74 - 2.96)</td>
<td>2.77 (2.67 - 2.86)</td>
</tr>
<tr>
<td>DM+CVD</td>
<td>2.45 (2.39 - 2.51)</td>
<td>2.36 (2.30 - 2.42)</td>
<td>2.19 (2.13 - 2.25)</td>
</tr>
<tr>
<td>CKD+DM+CVD</td>
<td>4.07 (3.91 - 4.24)</td>
<td>3.57 (3.42 - 3.71)</td>
<td>3.25 (3.23 - 3.47)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.81 (0.80 - 0.82)</td>
<td>0.81 (0.80 - 0.83)</td>
<td>0.81 (0.80 - 0.83)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.70 (1.60 - 1.81)</td>
<td>1.79 (1.69 - 1.90)</td>
<td>1.84 (1.73 - 1.95)</td>
</tr>
<tr>
<td>GI disease</td>
<td>1.24 (1.21 - 1.28)</td>
<td>1.26 (1.22 - 1.30)</td>
<td>1.25 (1.21 - 1.29)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.86 (1.83 - 1.90)</td>
<td>1.84 (1.80 - 1.87)</td>
<td>1.80 (1.76 - 1.83)</td>
</tr>
<tr>
<td>COPD</td>
<td>1.98 (1.94 - 2.01)</td>
<td>1.96 (1.93 - 1.99)</td>
<td>1.95 (1.92 - 1.99)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.70 (1.67 - 1.73)</td>
<td>1.71 (1.68 - 1.74)</td>
<td>1.72 (1.69 - 1.75)</td>
</tr>
</tbody>
</table>
In this spread we assess the role of chronic kidney disease in the risk of stroke. We use Medicare data for patients 65 and older, and the Ingenix i3 database to look at younger CKD patients. The incidence of stroke is approximately 9 percent overall in new Medicare CKD patients, comparable to the rate reported in the 2006 ADR.

Among Medicare patients, rates of incident stroke are 1.9–3.6 times higher for those with incident CKD than in those without CKD, and twice as common in CKD Stage 5 patients among those with CKD of Stage 3. Remarkably, in the younger Ingenix i3 cohort, stroke is 4.6–7.6 times more frequent for incident CKD patients than for non-CKD patients, though the absolute incidence is lower when compared to the Medicare cohort. The incidence of stroke is also lower in the prevalent CKD cohort, but the relative effect of CKD is still strong. In both the incident and prevalent CKD cohorts, the risk of stroke increases with age and CKD stage.

CKD increases the risk of incident stroke by more than 50 percent in the Medicare population, but its relative effect in the younger Ingenix i3 population is almost two-fold greater, with an associated hazard ratio of 2.32. This increased relative effect of CKD on the risk of stroke in the Ingenix i3 data is present with any combination of CKD, diabetes, and cardiovascular disease. Risk of stroke is 50 percent higher for African Americans compared to white Medicare beneficiaries, similar to previous observational studies. These data suggest that we should be targeting younger CKD patients with aggressive stroke prevention efforts. Figures 5.23–24 & Table 5.4; see page 146 for analytical methods. Incident & prevalent Medicare (age 65 & older) & Ingenix i3 (age 50–64) patients with or without CKD or stroke in 2005; CKD & stroke identified in 2006.
The incidence of stroke in CKD patients begins rising steeply three months prior to ESRD initiation, peaks at initiation or slightly after, and then subsides. Survival bias prior to initiation, and high mortality due to stroke after initiation, clearly contribute to this pattern, but the process of dialysis may also play a strong role. 

Cumulative probability of death twelve months after stroke in patients with or without CKD, by age & diabetic status, 2006. The cumulative probability of death twelve months after stroke in CKD patients and in those with CKD and diabetes, age 65–74, is twice that of non-CKD patients and of patients with CKD but no diabetes. Among patients age 85 and older with both CKD and diabetes, only 48 percent are alive at six months after a stroke, and only 38 percent at one year, compared to 66 and 57 percent of non-CKD patients, respectively. 

Prevalent CKD patients age 65 & older, 2005; incident stroke identified in 2006. 

CKD stage markers
1. eGFR ≥90, albumin/creatinine ratio (ACR) ≥30 mg/g
2. eGFR 60–89, ACR ≥30 mg/g
3. eGFR 30–59
4. eGFR 15–29
5. eGFR <15 (dialysis pts excluded from analyses)
The risk of HOSPITALIZATION is three times greater in patients with CKD, diabetes, & CVD than in patients with none of these conditions. • 5.a

In 2007, patients with COPD & Stage 4–5 CKD had an adjusted hospitalization rate of 705 per 1,000 patient years. • 5.2

Since 2004, rates of hospitalization for INFECTION have increased 6.4% among Ingenix i3 patients. • 5.5

Hospitalization rates for PNEUMONIA in Medicare CKD patients have fallen 33.4% since 1995. • 5.10

Rates of hospitalization for bacteremia/septicemia in Medicare CKD patients are 11.5% higher than in 1995. • 5.11

At 7.8 per 1,000 patient years, hospitalizations for pneumonia in MarketScan CKD patients are 67% lower than in their Medicare counterparts. • 5.13

Adjustments for patient COMPLEXITY imply that decreasing comorbidity & severity of disease may explain part of the decline in mortality. • 5.19–21

The RISK OF DEATH is three times greater for patients with CKD, diabetes, & CVD than for patients without these conditions. • 5.b

The incidence of STROKE is approximately 9% overall in new Medicare CKD patients. • 5.23

African Americans are at a 50% increased risk of STROKE compared to other patients of other races. • 5.c

The risk of death after stroke in CKD patients is more than DOUBLE that of non-CKD patients. • 5.26

summary