chapter FIVE

cardiovascular disease in patients with chronic kidney disease

Give me my Romeo: and when he shall die, 
Take him and cut him out in little stars, 
And he will make the face of heaven so fine 
That all the world will be in love with night, 
And pay no worship to the garish sun

William Shakespeare, Romeo & Juliet
In this chapter we use Part D Medicare claims data to present a broad overview of medication use in elderly CKD patients who have a variety of cardiovascular conditions (CHF, AMI, PAD, CVA/TIA, and atrial fibrillation) or prior cardiovascular interventions (ICDs/CRT-Ds, PCI, and CABG). The usual caveats apply in review of these data: they are entirely observational, and the possibility of confounding must be considered in their interpretation.

Figure 5.1, with a slightly different focus than the figures that follow, provides data on medication use in CKD patients as a group rather than related to specific cardiovascular diseases. On the left are agents commonly used to treat a variety of conditions: CHF, AMI, hypertension, atrial fibrillation, and ischemic heart disease. These agents are also frequently employed in patients receiving defibrillators and coronary revascularization, many of whom have comorbid cardiovascular conditions. The right side focuses on anti-platelet agents. Pentoxifylline and cilostazol are predominantly restricted for the clinical indication of PAD, while clopidogrel is widely used in patients with coronary revascularization, AMI, PAD, cerebrovascular disease, and, to a lesser extent, atrial fibrillation.

Approximately 46 percent of all CKD patients are identified as being on an ACEI/ARB, and a nearly equal proportion (44 percent) are on beta blockers; 28 percent receive an ACEI/ARB and beta blocker concurrently. The proportion using prescription anti-platelet agents (not including aspirin, as it is not a prescription drug) is considerably lower; one possible clinical conjecture here is that PAD is undertreated in elderly CKD patients. In a group with heightened risk of atherosclerotic disease and PAD, overall use of cilostazol (one of the few agents shown to be of benefit in PAD) is low, at 1.2 percent of the entire CKD cohort.

On the next spread we examine the use of therapeutic agents and cardiac procedures (defibrillators and coronary revascularization) across cardiovascular diseases and CKD stage. One important limitation of these data is the ascertainment of drug use related to the cardiovascular condition. In this analysis, a time period of 30 days before and 30 days after diagnosis is used to identify medications related to the condition of interest. If the follow-up period was extended, the proportion of patients receiving each medication might be higher.
It is apparent that ACEIs/ARBs, beta blockers, and statins are widely used in CKD patients across the breadth of cardiovascular disease. The therapeutic armamentarium for many cardiovascular diseases (e.g., CHF, ischemic heart disease) is impressive, and the wide use of evidence-based therapies in part reflects the safety and efficacy of agents such as ACEIs/ARBs and beta blockers. In contrast, a limited number of medications have been shown to be of benefit in treating PAD. Perhaps more importantly, the overall perceived benefit (in the context of other treatment trials such as beta blockers for heart failure) is relatively modest. Even though cilostazol is approved to treat symptomatic PAD, less than 3 percent of patients in this sample identified with PAD were treated with this medication.

One potentially surprising finding is that, despite the potential concerns related to CKD and use of aldosterone antagonists, 7 percent of CHF patients with CKD of Stages 3–5 are identified as receiving spironolactone.

In the next spread we update data on the importance of CKD as a predictor of increased mortality risk among patients with cardiovascular disease, adding new figures on the probability of rehospitalization and rehospitalization/death. And in the remaining spreads we explore geographic variations in rates of cardiovascular disease in CKD and non-CKD patients, look at state-level differences in the use of prescription medications to treat CHF and atrial fibrillation, and show the percentage of CKD and non-CKD patients treated for CHF, AMI, and atrial fibrillation.

*Figure 5.1; see page 169 for analytical methods. January 1 prevalent Medicare patients age 66 & older, 2007.*
### Prescription drug therapy in patients with cardiovascular disease (percent), by CKD status & diagnosis code, 2007

<table>
<thead>
<tr>
<th>Condition</th>
<th>CHF</th>
<th>AMI</th>
<th>PAD</th>
<th>CVA/TIA</th>
<th>AFIB</th>
<th>ICD/CRT-D</th>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CKD claim</td>
<td>57,674</td>
<td>993</td>
<td>4,821</td>
<td>7,278</td>
<td>3,749</td>
<td>832</td>
<td>3,743</td>
<td>5,945</td>
</tr>
<tr>
<td>$585.1-2</td>
<td>41.4</td>
<td>40.6</td>
<td>38.5</td>
<td>38.8</td>
<td>50.3</td>
<td>40.5</td>
<td>41.0</td>
<td>42.2</td>
</tr>
<tr>
<td>$585.3-5</td>
<td>40.6</td>
<td>45.9</td>
<td>49.6</td>
<td>44.2</td>
<td>57.3</td>
<td>59.5</td>
<td>45.8</td>
<td>51.8</td>
</tr>
<tr>
<td>$585.9/other</td>
<td>14.5</td>
<td>12.0</td>
<td>10.9</td>
<td>13.6</td>
<td>8.1</td>
<td>9.7</td>
<td>6.8</td>
<td>11.5</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>6.6</td>
<td>7.7</td>
<td>7.1</td>
<td>7.9</td>
<td>4.6</td>
<td>3.2</td>
<td>4.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Digoxin</td>
<td>10.6</td>
<td>14.8</td>
<td>15.4</td>
<td>13.8</td>
<td>3.9</td>
<td>17.5</td>
<td>35.4</td>
<td>30.8</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>17.5</td>
<td>16.3</td>
<td>15.9</td>
<td>16.7</td>
<td>11.0</td>
<td>16.1</td>
<td>11.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>0.6</td>
<td>1.0</td>
<td>1.1</td>
<td>0.9</td>
<td>0.7</td>
<td>1.6</td>
<td>1.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.6</td>
<td>0.1</td>
<td>0.8</td>
<td>0.7</td>
<td>0.2</td>
<td>1.2</td>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0.8</td>
<td>1.1</td>
<td>0.9</td>
<td>1.1</td>
<td>0.8</td>
<td>1.2</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>3.9</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
<td>0.6</td>
<td>1.8</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>4.4</td>
<td>4.8</td>
<td>4.2</td>
<td>4.0</td>
<td>4.1</td>
<td>3.7</td>
<td>3.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>3.9</td>
<td>3.7</td>
<td>3.9</td>
<td>3.9</td>
<td>3.7</td>
<td>3.7</td>
<td>3.9</td>
<td>2.9</td>
</tr>
</tbody>
</table>
Data here show that use of ACEIs/ARBs in patients with congestive heart failure is consistent across CKD stage. In patients with myocardial infarction, there is apparent underuse of combined ACEI/ARB and beta blocker therapy in relation to CKD; 42 percent of non-CKD patients receive combination therapy, compared to 34–36 percent of those with some identified stage of CKD.

Likely reflecting clinical trial data, warfarin is commonly used in elderly patients with atrial fibrillation (AFIB). About 44 percent of non-CKD patients receive warfarin as part of their AFIB treatment, compared to 38–39 percent of patients with some identified stage of CKD. Interestingly, 12 percent of AFIB patients with Stage 3–5 CKD are identified as receiving amiodarone.

Warfarin use in patients with CVA/TIA is low, at just 13 percent (only patients with ischemic stroke, however, are appropriate candidates, and this analysis does not specify stroke type). As aspirin is not a prescription agent, we have no information regarding aspirin therapy. Aggrenox, a prescription drug employing a fixed combination of aspirin and dipyridamole in an extended release preparation, is used in approximately 2 percent of CKD patients. Regimens containing clopidogrel are used in about 21 percent of patients with Stage 3–5 CKD. Aspirin and dipyridamole in an extended release preparation, as aspirin is not a prescription agent, we have no information regarding aspirin therapy. Aggrenox, a prescription drug employing a fixed combination of aspirin and dipyridamole in an extended release preparation, is used in approximately 2 percent of CKD patients. Regimens containing clopidogrel are used in about 21 percent of patients with Stage 3–5 CKD.

**ICD-9-CM codes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>585.1</td>
<td>Chronic kidney disease, Stage 1</td>
</tr>
<tr>
<td>585.2</td>
<td>Chronic kidney disease, Stage 2 (mild)</td>
</tr>
<tr>
<td>585.3</td>
<td>Chronic kidney disease, Stage 3 (moderate)</td>
</tr>
<tr>
<td>585.4</td>
<td>Chronic kidney disease, Stage 4 (severe)</td>
</tr>
<tr>
<td>585.5</td>
<td>Chronic kidney disease, Stage 5 (excludes 585.6: Stage 5, requiring chronic dialysis.)</td>
</tr>
<tr>
<td>585.9/oth.</td>
<td>Chronic kidney disease, unspecified</td>
</tr>
</tbody>
</table>

In USRDS analyses, patients with ICD-9-CM code 585.6 are considered to have code 585.5, see Appendix A for details.

CKD stage estimates are from a single measurement. For clinical case definition, abnormalities should be present ≥ 3 months.

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**Prescription drug therapy in patients with CHF, by CKD diagnosis code, 2007**

- ACEI/ARB alone
- Beta blocker alone
- Both

**Prescription drug therapy in patients with AMI, by CKD diagnosis code, 2007**

- ACEI/ARB alone
- Beta blocker alone
- Both

**Prescription drug therapy in patients with atrial fibrillation, by CKD diagnosis code, 2007**

- Warfarin alone
- Clopidogrel alone
- Warfarin & Clopidogrel
- Amiodarone

**Prescription drug therapy in patients with CVA/TIA, by CKD diagnosis code, 2007**

- Warfarin alone
- Clopidogrel alone
- Warfarin & Clopidogrel
- Aggrenox

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**Prescription drug therapy in patients with CHF, by CKD diagnosis code, 2007**

- ACEI/ARB alone
- Beta blocker alone
- Both

No CKD claim          585.1-2 585.3-5 585.9/other

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Data here show that use of ACEIs/ARBs in patients with congestive heart failure is consistent across CKD stage. In patients with myocardial infarction, there is apparent underuse of combined ACEI/ARB and beta blocker therapy in relation to CKD; 42 percent of non-CKD patients receive combination therapy, compared to 34–36 percent of those with some identified stage of CKD.

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**Prescription drug therapy in patients with CHF, by CKD diagnosis code, 2007**

- ACEI/ARB alone
- Beta blocker alone
- Both

No CKD claim          585.1-2 585.3-5 585.9/other

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**Prescription drug therapy in patients with AMI, by CKD diagnosis code, 2007**

- ACEI/ARB alone
- Beta blocker alone
- Both

No CKD claim          585.1-2 585.3-5 585.9/other

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**Prescription drug therapy in patients with atrial fibrillation, by CKD diagnosis code, 2007**

- Warfarin alone
- Clopidogrel alone
- Warfarin & Clopidogrel
- Amiodarone

No CKD claim          585.1-2 585.3-5 585.9/other

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**Prescription drug therapy in patients with CVA/TIA, by CKD diagnosis code, 2007**

- Warfarin alone
- Clopidogrel alone
- Warfarin & Clopidogrel
- Aggrenox

No CKD claim          585.1-2 585.3-5 585.9/other
There is a graded mortality risk related to CKD severity among patients with cardiovascular disease. One-year mortality for CHF patients without identified CKD, for example, is 21 percent, compared to 27 percent for patients with Stage 3–5 CKD. For AMI, this risk reaches 36 and 51 percent, respectively; for atrial fibrillation, 20 and 35 percent; and for CVA/TIA, 14 and 26 percent.

The highest rehospitalization rate occurs following AMI, at 1,670 per 1,000 patient years. With the additional contribution of high mortality among CKD patients following AMI, the combined rehospitalization/death rate reaches 2,147. CHF is known to be associated with high rehospitalization rates among Medicare patients; interestingly, though, the rate for CKD patients with atrial fibrillation is identical to that of CHF patients, and the rate of rehospitalization/death is slightly higher. (Some of these conditions, such as atrial fibrillation and CHF, clearly coexist.) As evidenced by these data, atrial fibrillation in elderly CKD patients is rightly considered a predictor of very high cardiovascular morbidity and mortality. See Figures 5.6–7.1 for analytical methods & photo credits. Medicare patients age 66 & older with a first cardiovascular diagnosis in 2007–2008 (5.6). Medicare CKD patients age 66 & older with a first hospitalization for cardiovascular disease/procedure & discharged alive in 2007–2008 (5.7).

ICD-9-CM codes

- 585.1 Chronic kidney disease, Stage 1
- 585.2 Chronic kidney disease, Stage 2 (mild)
- 585.3 Chronic kidney disease, Stage 3 (moderate)
- 585.4 Chronic kidney disease, Stage 4 (severe)
- 585.5 Chronic kidney disease, Stage 5 (excludes 585.6; Stage 5, requiring chronic dialysis. *)
- 585.9/oth. Chronic kidney disease, unspecified

* In USRDS analyses, patients with ICD-9-CM code 585.6 are considered to have code 585.5; see Appendix A for details.

CKD stage estimates are from a single measurement. For clinical case definition, abnormalities should be present ≥ 3 months.
Here we examine the likelihood within one year of rehospitalization and rehospitalization/death. For non-CKD patients with CHF, the probabilities are 58 and 64 percent, respectively, compared to 68 and 73 percent for those with Stage 3–5 CKD. Rates of rehospitalization/death for patients with atrial fibrillation are comparable to those of CHF patients, likely a reflection of their similar cardiac comorbidity.

Comparing non-CKD patients to those with Stage 3–5 CKD, the probabilities of rehospitalization within six months are 41 and 55 percent for those with atrial fibrillation, and 37 versus 53 percent for those with CVA/TIA, while the probabilities of rehospitalization/death are 46 and 63 percent for those with atrial fibrillation, and 43 versus 60 percent for those with CVA/TIA. See page 170 for analytical methods. Medicare patients age 66 & older with a first hospitalization for cardiovascular disease & discharged alive in 2007–2008.
The overall geographic pattern of CHF across the country is similar for elderly patients with and without CKD. Absolute event rates, however, are strikingly different, at 329 per 1,000 patient years for CKD patients, compared to just 97 for those without the disease. Geographic clustering of CHF includes the southern part of the U.S. and Appalachia.

The same type of clustering appears for CVA/TIA. For CKD patients, the overall rate is 153 events per 1,000 patient years among CKD patients, compared to 80 among their non-CKD counterparts. There is considerable geographic overlap for CHF and CVA/TIA, unsurprising given that both conditions share similar cardiovascular risk factors (particularly hypertension). \( \text{FIGURES 5.9-10; see page 170 for analytical methods.} \)
The overall rate of AMI is 11 per 1,000 patient years for non-CKD patients, compared to 30 for CKD patients. Geographic variations are similar for both populations, with higher rates of AMI in some northern and Midwestern regions, in Appalachia, and in the South.

The overall rate of cardiac arrest for non-CKD patients is 7.8 per 1,000 patient years, while the rate is nearly three times higher for those with CKD, at 22.3.

Data here should be viewed in relation to the maps on the following spread, showing geographic variations in the treatment of CHF and atrial fibrillation.

*Figures 5.11-12; see page 170 for analytical methods. December 31, 2007 point prevalent Medicare patients age 66 & older.*
Figures 5.13–14 are “mirror image” maps illustrating variations in the use of medications to treat congestive heart failure, specifically ACEIs/ARBs and beta blockers. Forty-two percent of non-CKD patients with CHF, for example, do not receive medications for their CHF, compared to 45 percent of CKD patients. *Figures 5.13–16; see page 170 for analytical methods.* January 1 point prevalent Medicare patients age 66 & older, with a first cardiovascular diagnosis or procedure between January 1 & November 30, 2007.
The percentages of non-CKD and CKD patients receiving both an ACEI/ARB and a beta blocker for CHF are identical, at 26.9. Forty-one percent of CKD patients with AMI receive an ACEI/ARB, compared to 50 percent of those without CKD; 35 and 42 percent, respectively, receive combined therapy.

Overall use of warfarin among patients with atrial fibrillation is higher among those without CKD, at 44.0 versus 38.2 percent, while use of clopidogrel and amiodarone is greater among those with CKD, at 11 versus 7 percent and 10 versus 7 percent, respectively. *Figures 5.17–19; see page 170 for analytical methods.*

January 1 point prevalent Medicare patients age 66 & older, with a first cardiovascular diagnosis or procedure between January 1 & November 30, 2007.
Approximately 46 percent of all CKD patients are identified as being on an ACEI/ARB, and a nearly equal proportion (44 percent) are on a beta blocker; 28 percent receive an ACEI/ARB and beta blocker concurrently. **Figure 5.1**

In patients with AMI, there is apparent underuse of combined ACEI/ARB and beta blocker therapy in relation to CKD; 42 percent of non-CKD patients receive combination therapy, compared to 34–36 percent of those with some identified stage of CKD. **Figure 5.3**

About 44 percent of non-CKD patients receive warfarin as part of their AFIB treatment, compared to 38–39 percent of patients with identified CKD. **Figure 5.4**

There is a graded mortality risk related to CKD severity among patients with cardiovascular disease. One-year mortality for CHF patients without identified CKD is 21 percent, compared to 27 percent for patients with Stage 3–5 CKD. For AMI, this risk reaches 36 and 51 percent, respectively; for atrial fibrillation, 20 and 35 percent; and for CVA/TIA, 14 and 26 percent. **Figure 5.6**

The geographic pattern of CHF across the country is similar for elderly patients with and without CKD. Absolute event rates, however, are strikingly different, at 329 per 1,000 patient years for CKD patients, compared to just 97 for those without the disease. **Figure 5.9**

The percentages of non-CKD and CKD patients receiving both an ACEI/ARB and a beta blocker for CHF are identical, at 26.9. **Figure 5.17**