Mount Rainier National Park, Washington

CARDIOVASCULAR DISEASE
This year’s chapter on cardiovascular disease in ESRD patients covers a number of topics new to the ADR.

The Cardiovascular Special Studies Center (CVSSC) has, for example, examined sudden cardiac death (SCD) in past ADRs, describing its epidemiology and preventative treatment — notably the use of implantable cardioverter defibrillators (ICDs). In this ADR we present new data on the occurrence of SCD in incident dialysis patients.

It has been appreciated for many years that the mortality rate in patients starting dialysis is considerably higher than in the prevalent dialysis population, but few data have been available on cause-specific mortality, particularly on SCD. On the next page we show that, despite the heightened rate of SCD in incident patients, the overall contribution of arrhythmic mechanisms as a percentage of attributable mortality is actually lower in incident than in prevalent patients. Twenty-four percent of incident patient deaths are attributed to arrhythmic mechanisms, compared to 30 percent in the prevalent population.

Another important issue is the relative imprecision of the method used to estimate SCD rates. In the 2006 ADR, we presented a new method designed to increase the level of precision above that obtained by using only data from the ESRD Death Notification form (CMS-2746). Here we illustrate long-term temporal trends in SCD, comparing the “new” or “complex” (Pun et al.) method to the “old” or “simple” method.

Expanding the analyses of prior ADRs on the epidemiology of SCD, we frame these data with information on new therapies designed to reduce the risk of SCD. We have previously looked at the use of ICDs and cardiac resynchronization-defibrillator devices (CRT-Ds), and at survival in the ESRD population following their implantation. The use in ESRD patients of wearable cardioverter defibrillators (WCDs), a “niche” therapy available in the U.S. for a decade, has, however, received little attention. In this ADR we present the first long-term survival data for a small number of dialysis patients who have received WCDs.

One long-time interest of the CVSSC is the persistently high mortality following AMI in dialysis patients. Despite improvements in survival after AMI in the general population, the two-year mortality rate among 2008 dialysis patients was 71.5 percent, nearly identical to the 73 percent reported fourteen years ago (Herzog et al.). Later in the chapter we examine fatal versus non-fatal AMI in ESRD patients; the estimation of fatal and non-fatal cardiovascular endpoints is an important issue on which there has been little data published.

Non-invasive and invasive cardiac evaluations are an important component of the care of ESRD patients, with respect both to diagnosis and treatment in dialysis patients and to the pre-transplant evaluation of renal transplant candidates. Guideline 1.1a of the National Kidney Foundation KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients recommends that a resting echocardiogram “be performed in all patients at the initiation of dialysis (pediatric or adult), once the patient has achieved dry weight, ideally within one to three months of dialysis initiation.” We present data addressing the use of echocardiography in incident dialysis patients, and on stress testing and angiography in incident dialysis patients and patients wait-listed for a renal transplant.

Finally, a key component of the treatment of cardiovascular disease in ESRD patients is their medical therapy. On the last spread we look at medication use and at survival associated with treatment. Figure 4.1; see page 435 for analytical methods.
Causes of death in incident & prevalent dialysis patients, 2008–2010
This figure uses the old/simple method and the new/complex method to estimate SCD rates in prevalent dialysis patients. The complex method yields a consistently lower rate for the past decade, an important consideration in clinical trial design. One important factor in this difference is the number of patients withdrawn from dialysis, a major cause of death which does not figure in clinical trials in the general population. 

Between 2000 and 2010, the rate of SCD in hemodialysis patients fell from 70 to 50 per 1,000 patient years, a decline mirrored in the peritoneal dialysis population. The largest absolute decline has occurred in the populations at highest risk of sudden cardiac death — those of older age, white race, or with diabetes. In patients 75 or older, for example, the rate fell from 111 to 75. There are many potential explanations for this striking temporal trend, but one possible contributor is the rapid expansion in the use of beta blockers. 

CARDIOVASCULAR DISEASE
sudden cardiac death in incident & prevalent dialysis patients
In comparison to the marked reduction in SCD in prevalent dialysis patients (Figures 4.3–6), the reduction in the rates of SCD in the first 90 days of therapy is relatively modest. Between 2005 and 2009 this rate fell only 10 percent, from 105 to 96. The first 90 days after dialysis initiation constitute a period of heightened SCD risk. » Figure 4.7; see page 435 for analytical methods. Incident dialysis patients age 20 & older; unadjusted, & using the simple method.

Even with the heightened risk of SCD in incident patients, the majority of deaths in the first year of dialysis are non-cardiovascular. White patients, not surprisingly, have the highest risk by race of SCD; it is surprising, however, that patients with diabetic ESRD do not have the highest risk by diagnosis, as they do in the prevalent population. While the risk of SCD is fairly uniform for peritoneal dialysis patients in the first year of therapy, the first 90 days are a period of increased risk for hemodialysis patients. It is tempting to attribute this difference to the acute hemodynamic stress associated with hemodialysis initiation and the much larger acute potassium shifts accompanying thrice-weekly hemodialysis in patients who may have been chronically hyperkalemic before initiation. It would be very interesting if data of this type were also available on patients receiving frequent or long-duration dialysis, as a lower risk of SCD in incident dialysis patients might be anticipated. » Figures 4.8–12; see page 435 for analytical methods. Incident dialysis patients age 20 & older; simple method.
Figures 4.13–14 document both the increasing numbers of dialysis patients receiving ICD/CRT-D devices and the overall decline in use after 2006, similar to that seen in the general population. From 1991 through 2010, we estimate that 12,984 unique dialysis patients received an ICD/CRT-D device, with 3,191 of these patients receiving a CRT-D device.

Two-year mortality in dialysis patients after the implantation of ICDs/CRT-Ds is high, reaching 53 percent following implantation for primary prevention and nearly 58 percent after implantation for secondary prevention. The two-year mortality for a transplant patient in the primary prevention group, in contrast, is 34 percent.

While WCDs have been used in over 60,000 U.S. patients in the last decade, there are few data on the use of this device in dialysis patients. Figures 4.15 and 4.17 present data on these patients and their associated survival. »Figures 4.13–17; see page 435 for analytical methods. Period prevalent patients: dialysis patients (4.13); dialysis & transplant patients in each year (4.14); dialysis patients (4.15); dialysis & transplant patients receiving their first ICDs/CRT-Ds in 1999–2010 (4.16); dialysis patients receiving their first WCDs in 2005–2010 (4.17).
Table 4.a presents a 15-year temporal analysis of cardiovascular conditions and cardiac revascularization procedures in ESRD patients, showing congestive heart failure and peripheral arterial disease as the two conditions with the highest prevalent rates.

Figures 4.18–19 provide new data on the epidemiology of AMI in ESRD patients, showing, for example, the apparent, counterintuitive occurrence of declining rates of fatal AMI and the simultaneous growth in rates of non-fatal AMI. It is tempting to attribute the increase in non-fatal AMI to the use of increasingly more sensitive biomarkers for diagnosis, such as cardiac troponins. The decline in fatal AMI may also be related to improvements in cardiovascular outcomes in ESRD patients, as well as to changing definitions (described in the appendix).

Since 1993, outcomes for dialysis patients after AMI have been consistently poor. One cause for optimism, however, is the improvement in 30-day mortality, from 35 percent in 1993 to 25 percent in 2008. While initial treatment has probably improved patient outcomes, much attention needs to be directed to long-term (i.e., post-discharge) treatment and survival. » Table 4.a & Figures 4.18–19; see page 435 for analytical methods. Point prevalent ESRD patients on January 1 of each year, age 20 & older; unadjusted (4.a & 4.18). Period prevalent dialysis patients with first AMI in the year, unadjusted (4.19).
Among 2010 incident dialysis patients age 65 and older, the cumulative percentage receiving an echocardiogram in the first year reached 60 percent, compared to 20 and 14 percent for stress tests and invasive coronary angiography, but only 0.2 percent for non-invasive angiography. The very low rate of non-invasive coronary angiography use probably reflects both the new Medicare reimbursement for this procedure and the technical difficulty of performing it in dialysis patients, due to the large burden of coronary calcification. » Figures 4.20–23; see page 435 for analytical methods. Incident dialysis patients, 2010.
In 2000, approximately 17 percent of prevalent dialysis patients received a stress test in the first year of therapy, compared to 22 percent in 2005 and 19 percent in 2010. Forty-two percent of patients wait-listed for a transplant in 2010 had a stress test in the year prior to listing, a modest reduction from the 47 percent seen in patients listed in 2005.

The use of echocardiography, in contrast, has been on the rise. In prevalent dialysis patients, the cumulative percentage receiving an echocardiogram has increased from 40 percent in 2000 to 48 and 51 percent in 2005 and 2010. In the year prior to wait-listing for a transplant, the number has increased from 43 percent in 2000 to 48 percent in 2005 and 53 percent in 2010. With the small decline in the use of stress testing in dialysis patients, one explanation might be an increase in the use of coronary angiography, but data here show that very few prevalent dialysis patients or patients wait-listed for a transplant receive non-invasive CT coronary angiograms.

One issue related to the use of angiography in the screening of renal transplant candidates has been the issue of preemptive transplantation. Patients with declining renal function not yet requiring dialysis therapy may be considered for both preemptive renal transplantation or, lacking an available kidney donor, “preemptive” wait-listing. It is likely that concerns related to the risk of contrast nephropathy, and the precipitation of AKI requiring emergency dialysis, still temper the use of diagnostic coronary angiography in patients being screened for renal transplantation but who do not yet require dialysis. » Figures 4.24–27; see page 435 for analytical methods.

Point prevalent dialysis patients & Medicare enrollees wait-listed for the first time.
### Table 4.4

**Cardiovascular disease & pharmacological interventions, by diagnosis & modality (row percent)**

<table>
<thead>
<tr>
<th></th>
<th>2007 N</th>
<th>ACEI/ARB</th>
<th>Beta blocker</th>
<th>Clopidogrel</th>
<th>Warfarin</th>
<th>Statin</th>
<th>Amiodarone</th>
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<tr>
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<td>41.2</td>
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<td>16.6</td>
<td>12.3</td>
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<td>70.0</td>
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<td>17.3</td>
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<td>89.6</td>
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<td>9.5</td>
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<tr>
<td>Peritoneal</td>
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<td>49.7</td>
<td>72.6</td>
<td>85.8</td>
<td>4.1</td>
<td>59.9</td>
<td>6.1</td>
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<td>296</td>
<td>49.7</td>
<td>76.4</td>
<td>86.5</td>
<td>12.2</td>
<td>70.6</td>
<td>3.4</td>
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<td><strong>Revascularization: CABG</strong></td>
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<td>Hemodialysis</td>
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<td>58.0</td>
<td>77.2</td>
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<td>10.1</td>
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<td>38</td>
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<td>32.2</td>
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<td>33.7</td>
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<tr>
<td>Transplant</td>
<td>27,035</td>
<td>41.9</td>
<td>53.9</td>
<td>3.7</td>
<td>4.7</td>
<td>47.6</td>
<td>0.4</td>
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</table>

2012 USRDS Annual Data Report

**Two-thirds of dialysis patients diagnosed with CHF in 2010 received a beta blocker, while 47 percent of hemodialysis patients with this diagnosis received an ACEI/ARB. Beta blockers were used by more than three-quarters of ESRD patients with an AMI during 2010 and, remarkably, by 58 percent of hemodialysis patients with no cardiovascular diagnosis or intervention. At least with respect to medical therapy with beta blockers, if therapeutic nihilism in dialysis patients is not dead, it would certainly appear to be moribund. This is not to say that ESRD patients uniformly receive therapies to the same degree as patients in the general population, but, at least with respect to certain evidence-based therapies, such as beta blockers, the gap in utilization is markedly smaller than it was a decade ago.**

The use of warfarin in hemodialysis patients with atrial fibrillation remains relatively low, perhaps reflecting concerns related to hemorrhagic risk in these patients. And given the relative paucity of data on amiodarone therapy in this population, the rates of amiodarone use for atrial fibrillation are perhaps higher than would be expected.

Finally, despite the publication of the 4D and AURORA trials, there has been no discernible reduction in the use of statin therapy in U.S. dialysis patients. To the contrary, even in those without identified prevalent cardiovascular illness, 28 percent of hemodialysis patients and 34 percent of peritoneal dialysis patients in 2007 received statins, compared to 34 and 40 percent in 2010. In the population qualifying for secondary prevention (e.g., those with an AMI), the use of statin therapy in hemodialysis patients increased from 55 percent in 2007 to 62 percent in 2010. » Table 4.4; see page 435 for analytical methods. January 1 point prevalent patients with Medicare Parts A, B, & D enrollment, with a first cardiovascular diagnosis or procedure in the year.

**CARDIOVASCULAR DISEASE medication & survival in ESRD patients with cardiovascular disease**
After AMI or a diagnosis of CHF, the number of ESRD patients receiving a beta blocker rose from 59 percent in 2007 to 65 percent in 2010. Use of ACEIs/ARBs declined slightly.

Data on the incidence of death and cardiovascular hospitalization following AMI or a diagnosis of CHF should be interpreted with caution, as there may be an element of selection bias. It is interesting to note, however, that the highest risk of death occurs in patients receiving no therapy. After a diagnosis of CHF, mortality among patients receiving combined therapy with ACEIs/ARBs and beta blockers was 19 percent, compared to 26 percent among those receiving no therapy; following AMI, these rates were 33 and 43 percent.

Different patterns occur for cardiovascular disease hospitalizations. It is possible that the increased incidence of hospitalizations may paradoxically relate in part to improved survival in patients receiving these beneficial therapies. » Figures 4.28–30: see page 435 for analytical methods. 

January 1 point prevalent ESRD patients with Medicare Parts A, B, & D enrollment, with a first diagnosis of CHF or AMI in the year.
CARDIOVASCULAR OUTCOMES

Outcomes at two years following a diagnosis of CHF (cumulative incidence; Figure 4.29)

- Death
  - ACEI/ARB: 0.38
  - Beta blocker: 0.37
  - Both: 0.35
  - Neither: 0.43
- Cardiovascular hospitalization
  - 0.53
  - 0.53
  - 0.57
  - 0.49

Outcomes at two years following a diagnosis of AMI (cumulative incidence; Figure 4.30)

- Death
  - ACEI/ARB: 0.55
  - Beta blocker: 0.54
  - Both: 0.51
  - Neither: 0.60
- Cardiovascular hospitalization
  - 0.59
  - 0.58
  - 0.64
  - 0.56

MEDICATION USE

Pharmacological intervention following a diagnosis of CHF, 2010 (percent of patients on medication; Table 4.c)

- Hemodialysis
  - ACEI/ARB: 46.6
  - Beta blocker: 66.0
  - Clopidogrel: 21.7
  - Statin: 42.7
- Peritoneal dialysis
  - 45.2
  - 67.2
  - 21.2
  - 48.6
- Transplant
  - 42.2
  - 76.3
  - 16.7
  - 58.5

Pharmacological intervention following a diagnosis of AMI, 2010 (percent of patients on medication; Table 4.c)

- Hemodialysis
  - ACEI/ARB: 55.6
  - Beta blocker: 76.9
  - Clopidogrel: 51.2
  - Statin: 61.9
- Peritoneal dialysis
  - 52.8
  - 78.2
  - 61.1
  - 69.9
- Transplant
  - 48.6
  - 87.1
  - 54.0
  - 77.6

Pharmacological intervention following a diagnosis of CVA/TIA (percent of patients on medication; Table 4.c)

- Hemodialysis
  - ACEI/ARB: 46.4
  - Beta blocker: 63.4
  - Clopidogrel: 27.2
  - Statin: 47.8
- Peritoneal dialysis
  - 46.0
  - 59.2
  - 27.2
  - 51.5
- Transplant
  - 41.2
  - 66.6
  - 22.6
  - 63.3