over the past few years, controversy over the definition and classification of chronic kidney disease (CKD) has played out in the editorial pages of nephrology journals. Although the debate occurred primarily among nephrologists, the controversy has implications for the care of CKD across all disciplines of medicine. A recently reached consensus on re-
visions to the classification of CKD based on pro-gnos
sis may help to quell the controversy. The revisions do not change the definition of CKD.

The revisions arose from a Controversy

Series Conference on "Chronic Kidney Disease: Definition, Classification and Prognosis" sponsored by Kidney Disease Improving Global Outcomes (KDIGO). KDIGO is an international nonprofit organization whose purpose is to improve the care and outcomes of kidney disease patients worldwide by promoting collaboration, coordination, and integration of initiatives to develop and implement clinical prac-
tice guidelines.

Before the conference, held in Oct-

ber, widespread agreement existed that kidney failure (stage 5 CKD) is a life-threatening condition, with in-
creasing prevalence around the world, high cost, and poor outcomes. In the United States, the prevalence of kidney disease treated by dialysis and transplantation is approximately 0.2 percent of the population (500,000 people), with an annual cost of $35 billion. Kidney disease is silent in its early stages, but can be detected by commonly available laboratory tests, such as creatinine to estimate glomerular filtration rate (GFR) and urinary albumin-to-
creatinine ratio (ACR) as a marker of kidney damage. Earlier detection and treatment could potentially reduce disease complications and the risk of develop-
ing kidney failure.

The controversies aired at the confer-
ence centered on the current definition and classification of chronic kidney disease (CKD) (Figure 2). KDIGO Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002 and subsequently adopted, with minor modi-
fications, by KDIGO in 2005. The KDIGO guidelines define CKD as either GFR <60 mL/min/1.73 m2 (less than half of the normal level in young adults) or kid-
ey damage (for >3 months) regardless of cause of disease. A urine albumin-to-
creatinine ratio >30 mg/g is defined as a marker of kidney damage.

In people with CKD, the disease is

Table 1: Adverse Reactions to Feraheme Reported in 605 Patients with CKD

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Feraheme (n = 605)</th>
<th>Oral Iron (n = 241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2.5%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.0%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.8%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Rash</td>
<td>0.8%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.8%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

In clinical trials, adverse reactions leading to treatment discontinuation and/or a 5% increase in total body iron content included hypotension, infusion site swelling, increased serum ferritin, chest pain, abdominal pain, syncope, angina, chest pain, and anxiety.

Following completion of the controlled phase of the trials, 605 patients received two additional 510 mg intravenous injections of Feraheme (the total cumulative dose of 2.04 g). Adverse reactions following the repeat Feraheme dosing were similar in character and frequency to those observed following the first two intravenous injections.

In a pseudo-controlled, cross-over trial, 713 patients with CKD received a single 510 mg dose of Feraheme. Adverse reactions reported by these patients were similar in character and frequency to those observed in either clinical trials.

DRUG INTERACTIONS

Drug-drug interaction studies with Feraheme were not conducted. Feraheme may reduce the absorption of concurrently administered and iron precursors.

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The debate reflects...a paradigm shift...from kidney failure as a life-threatening illness to earlier stages of kidney disease as the target for prevention, detection, evaluation, and management. —Andrew Levey

Further classified by the level of GFR (known as stages). Population surveys of estimated GFR and urinary ACR identify between 11 and 12 percent of the U.S. adult population as having CKD using this definition (23 million people). The prevalence of CKD is as high as 40 percent among people over 70, primarily because of the large number of people with GFR 30–59 mL/min/1.73 m² (CKD stage 3), many of whom do not have elevated ACR. The prognosis of earlier stages of CKD is highly variable, with more people dying of cardiovascular disease (CVD) than kidney failure.

Based on similar findings around the world, the International Society of Nephrology and International Federation of Kidney Foundations adopted the message for World Kidney Day in 2008 that “CKD is common, harmful, and treatable.” One of the purposes of the KDIGO conference was to identify absolute and relative risks of complications of CKD, including all-cause mortality, CVD mortality, kidney failure, acute kidney injury, and progressive kidney disease.

Overdiagnosis of CKD a concern

The main concern about the current definition and classification was the possibility of overdiagnosis of CKD and overuse of resources in the investigation and management of CKD, with our appropriate modifications for variations in prognosis. Specific issues raised were the appropriateness of the GFR thresholds, albuminuria thresholds, and absence of age modifications—since lower GFR levels and higher albumin excretion rates are commonly observed in the apparently “healthy” elderly. Underlying these controversies was concern regarding the methods for assessing eGFR and albuminuria, and discomfort with the term “disease” for labeling a large number of people, mostly elderly, with lower levels of GFR and albuminuria.

In response to this debate, the KDIGO Board of Directors convened the Controversies Conference to review and possibly suggest revisions to the definition and classification of CKD, in light of current knowledge regarding its prognosis, with the goal of improving patient outcomes. KDIGO appointed a Planning Committee chaired by Andrew Levey, MD (U.S.), and co-chaired by Meguid El Nahas, MD (U.K.), Paul de Jong, MD (NL), and Josef Coresh, MD, PhD (U.S.). The KDIGO Controversies Conference was tasked with addressing five questions:

1) What are the key outcomes of CKD?
2) What progress has been made in CKD testing (eGFR and albuminuria)?
3) What are the key factors determining prognosis of CKD (e.g., eGFR, albuminuria)?
4) Should the current CKD classification (based on eGFR) be modified to include additional factors associated with prognosis?
5) Should the current CKD definition be modified?

The planning committee invited representatives of studies to contribute data on outcomes of CKD in clinical or research populations in which eGFR and albuminuria had been determined at baseline. Outcomes considered included all-cause mortality, CVD mortality, kidney failure treated by dialysis or transplantation (end stage renal disease), acute kidney injury, and decline in eGFR (progressive CKD). An analytical committee provided a uniform analysis plan for systematic evaluation of the data for each cohort and performed meta-analyses of results provided by the studies.

Altogether, more than 50 cohorts submitted data and participated in the conference. Meta-analyses on 1.5 million study participants on a range of outcomes were performed and reviewed. A databook consisting of 1704 pages of cohort data and 464 pages of results of meta-analyses was distributed to all conference participants.

The conference consisted of plenary sessions during which KDIGO Co-Chairs Bertzam Kasiske, MD (U.S.), and Kai-Uwe Eckardt, MD (Germany), members of the Planning Committee, Richard Glassock, MD (U.S.), a noted critic of the current definition and classification, and other experts on CKD outlined the background and objectives of the conference. Following plenary sessions, conference participants broke out into smaller groups for in-depth discussions of data and a proposal for revisions, and then reconvened in a plenary session for expression of viewpoints on a number of subjects, including a non-binding vote on questions prepared by the organizers.

The data reviewed showed a strong, consistent gradation in risk for all outcomes of CKD according to the level of estimated GFR and urine ACR across a wide range of study populations. Interes-...