Clin Exp Nephrol (2008) 12:41–52
DOI 10.1007/s10157-007-0016-3

ORIGINAL ARTICLE

Delivery patterns of recommended chronic kidney disease care in clinical practice: administrative claims-based analysis and systematic literature review

Marie D. Philipneri · Lisa A. Rocca Rey · Mark A. Schnitzler · Kevin C. Abbott · Daniel C. Brennan · Steven K. Takemoto · Paula M. Buchanan · Thomas E. Burroughs · Lisa M. Willoughby · Krista L. Lentine

Received: 17 July 2007 / Accepted: 1 October 2007 / Published online: 5 January 2008

Abstract
Background Clinical practice guidelines for management of chronic kidney disease (CKD) have been developed within the Kidney Disease Outcomes Quality Initiative (K/DOQI). Adherence patterns may identify focus areas for quality improvement.
Methods We retrospectively studied contemporary CKD care patterns within a private health system in the United States, and systematically reviewed literature of reported practices internationally. Five hundred and nineteen patients with moderate CKD (estimated GFR 30–59 ml/min) using healthcare benefits in 2002–2005 were identified from administrative insurance records. Thirty-three relevant publications in 2000–2006 describing care in 77,588 CKD patients were reviewed. Baseline demographic traits and provider specialty were considered as correlates of delivered care. Testing consistent with K/DOQI guidelines and prevalence of angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) medication prescriptions were ascertained from billing claims. Care descriptions in the literature sample were based on medical charts, electronic records and/or claims.
Results KDOQI-consistent measurements of parathyroid hormone (7.1 vs. 0.6%, $P = 0.0002$), phosphorus (38.2 vs. 1.9%, $P < 0.0001$) and quantified urinary protein (23.8 vs. 9.4%, $P = 0.008$) were more common among CKD patients with versus without nephrology referral in the administrative data. Nephrology referral correlated with increased likelihood of testing for parathyroid hormone and phosphorus after adjustment for baseline patient factors. Use of ACEi/ARB medications was more common among patients with nephrology contact (50.0 vs. 30.0%; $P = 0.008$) but appeared largely driven by higher comorbidity burden. The literature review demonstrated similar practice patterns.
Conclusions Delivery of CKD care may be monitored by administrative data. There is opportunity for improvement in CKD guideline adherence in practice.

Keywords Angiotensin-converting enzyme inhibitors · Chronic kidney disease · Guideline adherence · Laboratory diagnoses · Physician's practice patterns · Referral and consultation

Funding Sources: Ms. Buchanan received support from a Public Policy Fellowship from the American Society of Transplantation. Dr. Brennan received support from a grant from the National Institute of Diabetes Digestive and Kidney Diseases (NIDDK), K24-DK002886. Dr. Lentine received support from a grant from the NIDDK, K08-DK073036.

M. D. Philipneri · K. L. Lentine
Division of Nephrology, Saint Louis University School of Medicine, St Louis, MO, USA

L. A. Rocca Rey · M. A. Schnitzler · S. K. Takemoto · P. M. Buchanan · T. E. Burroughs · L. M. Willoughby · K. L. Lentine (✉)
Saint Louis University Center for Outcomes Research, Saint Louis University School of Medicine, Salus Center 2nd Floor, 3545 Lafayette Avenue, St Louis, MO 63104, USA
e-mail: lentine.krista@stanfordalumni.org

L. A. Rocca Rey
Chair of Nephrology, San Paolo Hospital, University of Milan, Milan, Italy

K. C. Abbott
Nephrology Service, Walter Reed Army Medical Center, Washington, DC, USA

D. C. Brennan
Division of Nephrology, Washington University School of Medicine, St Louis, MO, USA

Introduction

Population based studies estimate that up to 19 million Americans have some form of chronic kidney disease (CKD) [1]. As a reflection of both of its prevalence and serious consequences, CKD has been named among the major focus areas of "Healthy People 2010" [2]. While there is mounting evidence for the value of timely and comprehensive CKD care [3–5], data have emerged suggesting patterns of suboptimal adherence to best practices. Some of the aspects of CKD care are particularly disregarded. For example, within the management of renal osteodystrophy, several recent studies report failure to monitor intact parathyroid hormone (iPTH) levels in approximately 85% or greater fractions of CKD patients [6–10].

In 2002, the National Kidney Foundation launched the promotion of clinical practice guidelines for diagnosis, evaluation and monitoring of CKD within the Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) in an effort to increase awareness of optimal CKD care [11]. As may be expected based on the focus areas in nephrology specialty practice, there is evidence supporting higher quality of CKD care and improved outcomes including survival among CKD patients who receive early referral to nephrologists [12–14]. Nonetheless, there may be opportunities to improve CKD care practices even among patients receiving specialty care [10, 15–18].

To enhance current understanding of the state of contemporary CKD care, we performed a retrospective study of the electronic records of a large health insurance provider describing the care of patients with moderate CKD from 2002 to 2005. We aimed to: (1) compare actual clinical practice with standards proposed by K/DOQI guidelines for measurement of proteinuria, parameters of bone and mineral metabolism, and serum lipids; (2) evaluate the use of medications blocking angiotensin II actions; and (3) assess variations in care according to nephrology referral status. We also performed a systematic literature review to frame our results in the context of reported care patterns worldwide.

Methods

Data source

Data were drawn from the de-identified, electronic records of a large health insurance provider in the Midwestern United States. Analyses were performed using Health information Portability and Accountability Act (HIPAA)-compliant, limited datasets from which all direct patient and provider identifiers were removed. This study was approved by the Institutional Review Board of Saint Louis University and by the research review board of the insurance provider.

Study sample

Eligible participants included insurance beneficiaries with at least one serum creatinine result in the ambulatory laboratory database during an enrollment window ranging from January 1, 2002 through March 31, 2004. The end of the enrollment window was chosen as one year before end date of available claims (March 31, 2005) at the time of the study. One year of continuous medical and pharmacy benefits eligibility following the index date was required, defined as coverage with unlimited gaps up to three days and/or a single gap of 4–60 days.

The date of the first serum creatinine within the observation window was taken as each participant's index date. We estimated glomerular filtration rate (GFR) from the index creatinine level by the abbreviated Modification of Diet in Renal Disease (aMDRD) equation [11], and classified CKD stage according to the schema of the NKF-K/DOQI [11]. All participants were assumed to be non-black, as race was not tracked in this administrative database. To restrict the sample to patients with pre-dialysis CKD, we excluded CKD patients with medical claims with International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes for dialysis and/or related complications prior to the index date (V56, 996.1, 996.56, 996.62, 996.68, 996.73, V45.1, E870.2, E871.2, E872.2, E874.2, E879.1).

Outcomes of interest

The primary outcomes were test performance within appropriate intervals following the index date according to the NKF-K/DOQI guidelines for characterization of CKD and important clinical complications [11, 19, 20]. Test performance was identified based on submission of dated medical claims with corresponding Current Procedural Terminology (CPT) codes as defined in Appendix 1. Outcomes of interest included: quantified urinary protein excretion; measurement of serum phosphorus, calcium, and iPTH levels; and lipid profiling. K/DOQI recommends proteinuria quantification as part of the characterization of CKD [11]. We considered testing for microalbuminuria or quantified proteinuria within one year of the index date as appropriate. In stage 3 CKD annual assessments of parameters of bone and mineral metabolism are advised [19]. Assessment of lipid status by a fasting, fractionated lipid panel is recommended in CKD care at initial presentation, upon change in lipid status or treatment, and annually [20]. We scored lipid testing as appropriate if performed within a 1-year period following the index date.

We also evaluated the use of Angiotensin Converting Enzyme inhibitor and Angiotensin Receptor Blockers (ACEi/

ARBs) medications based on submission of pharmacy claims with National Drug Codes for any drug of this class.

Co-morbid conditions and nephrology referral status

The presence of co-morbid conditions was defined based on medical claims with ICD-9-CM diagnostic codes for hypertension (401–405), diabetes mellitus (250, 357.2, 362.0, 366.41, 648.0) and congestive heart failure (428, 402.×1, 404.×1, 398.91). We identified patients with nephrology specialty encounters in the database based on submission of any medical claim with a corresponding nephrology provider specialty code. The comparison group comprised patients who had not seen a nephrologist during the study period.

Statistical analyses

Means and standard deviations were computed to describe continuous variables. Categorical variables were described with counts and proportions. We compared proportions of guideline consistent test performance and medication use according to nephrology referral status with two-sided Fisher's exact tests. Adjusted associations of baseline characteristics and nephrology referral status with guideline were modeled by multivariable logistic regression.

Systematic literature review

To frame our results in the context of reported care patterns, we performed a systematic literature search for studies describing frequencies of assessment of proteinuria, serum lipids and parameters of bone and mineral metabolism in patients with CKD. We limited our search to studies published between January 2000 and November 2006. Our search strategy included electronic queries of MEDLINE using the medical subject heading (MeSH) terms listed in Appendix 2. Articles describing pediatric populations or peculiar subgroups of subjects (e.g., hospitalized patients) were excluded. Manual search of the reference lists of relevant articles supplemented electronic findings. The descriptive and outcome data elements abstracted from the final sample of articles are provided in Tables 2 and 3.

Results

Participants

We identified 7,735 unique patients with at least one serum creatinine result within the study period. Of these, 4,748 patients had at least one year of continuous insurance benefits after the index date. Based on the aMDRD equation, the distribution of estimated GFR was: ≥90 ml/min, 1,355 patients; 60–89 ml/min, 2,809 patients; 30–59 ml/min, 519 patients. These latter 519 patients, classified as CKD stage 3, were selected for further study. To enable assessment of trends in practice patterns over time, we divided this sample into approximately halves according to index date falling prior to (N = 268) or after (N = 251) July 1, 2003, for certain sub-analyses.

The average participant age in our study sample was 57 years (range 15–91 years), and 62% were women. Comorbidity indications in claims included hypertension in 59%, diabetes in 21%, and congestive heart failure in 8%. Eight percent of subjects received a nephrology consultation during the observation period. As shown in Fig. 1, stage 3 CKD patients referred to nephrologists were noted to have a heavier burden of comorbidities. More than 30% of patients evaluated by nephrologists had both hypertension and diabetes, whereas approximately 40% of unreferred patients were without indications of hypertension, diabetes or heart failure in the database.

Prevalence and correlates of guideline-consistent CKD care

With the exception of lipid measurement, adequate diagnostic testing was significantly more common among CKD patients referred to nephrologists compared to those without referral (Fig. 2). Fractionated lipid assessment was performed in approximately 60% of patients and did not differ by specialty contact (P = 0.5). The prevalence of recommended testing for iPTH was very low regardless of referral status, being 7.1% in specialty-referred versus 0.6% in un-referred patients (P = 0.0002). Among

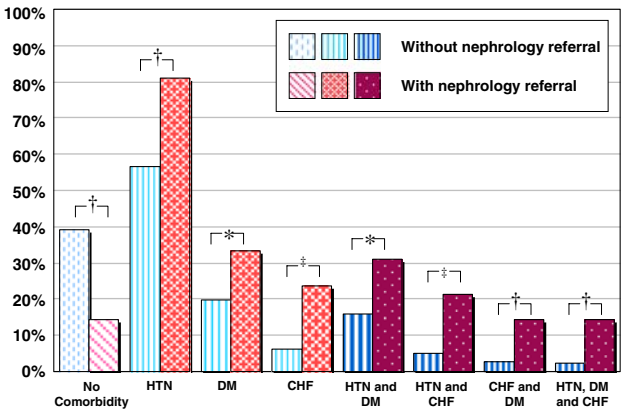

Fig. 1 Comorbidity distribution according to referral status in the study sample of patients with moderate (stage 3) CKD. *CKD* chronic kidney disease; *CHF* congestive heart failure; *DM* diabetes mellitus; *HTN* Hypertension. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$

specialty care recipients, only 38.2% underwent phosphorus measurement, although this was higher than observed in the sample without specialty care (1.9%, $P < 0.0001$). Calcium testing was common, but was higher among patients seen by specialists (82.4 vs. 97.6%, $P = 0.008$). Overall, urinary protein quantification was performed among 10.6% of the full study sample, comprising 23.8% of specialty-referred patients compared to 9.4% of non-referred subjects ($P = 0.008$). Within the full sample there was a pattern of increased quantification of urinary protein among the more recently enrolled compared to the earlier cohort (13.8 vs. 7.2%, $P = 0.01$). This pattern of increased urine protein measurement in the later compared to earlier study period was significant among patients without nephrology referral (12.2 vs. 6.5%, $P = 0.01$) and showed a non-significant trend within the small sample referred to nephrologists (30.4 vs. 15.8%, $P = 0.3$).

According to multivariate analysis (Table 1), aside from an association of male gender with increased odds of calcium measurement, care patterns were not predicted by baseline demographics. However, there were important associations of guideline consistency with comorbidities. Independent of gender, age and referral status, stage 3 CKD patients with diabetes or hypertension had higher odds of being tested for proteinuria, calcium and lipids. After adjustment for baseline demographics and comorbidity, nephrology referral strongly predicted increased likelihood of testing for iPTH and phosphorus.

Prescription patterns of ACE inhibitors/ARB medications

In the total CKD study sample, patients referred to nephrologists were prescribed ACEi/ARBs medications approximately 70% more often than those without specialty contact (prescribing prevalence 50.0 vs. 30.0%; $P = 0.008$) (Fig. 3). While not statistically significant, similar prescribing patterns according to referral status were observed among patients without major comorbidities (33.3 vs. 6.2%; $P = 0.06$). When comparing prescribing patterns within comorbidity-stratified samples, however, the frequency of use of ACEi/ARBs did not differ significantly according to referral, although there was a consistent trend towards slightly higher total prescribing among patients seen by nephrologists.

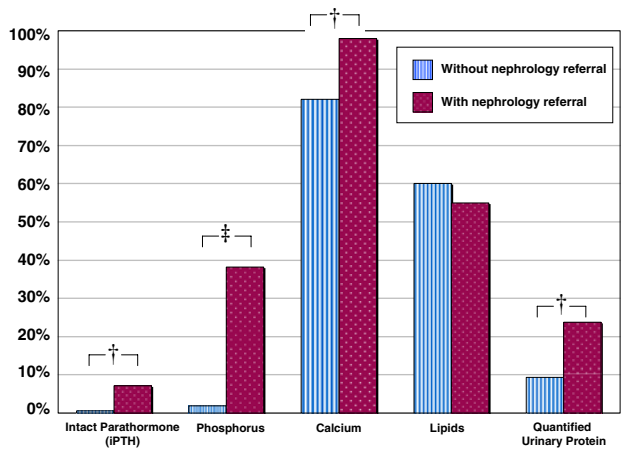

Fig. 2 Prevalence of guideline-consistent evaluation and monitoring, according to referral status, in the study sample of patients with moderate (stage 3) CKD. † $P < 0.01$; ‡ $P < 0.0001$

While the prevalence of ACEI/ARB use was higher in patients with relevant comorbidities, only 52.6% of CKD patients with hypertension and diabetes received treatment to block the rennin–angiotensin system during observation. Moreover, only 37.4% of the CKD patients with co-existing hypertension, diabetes and heart failure were treated with ACEI/ARBs. There was no difference in the prevalence of ACEI/ARB prescribing among earlier compared to later enrolled members of the full sample (31.5 vs. 31.7%, $P = 0.9$), nor were there temporal trends in the use of these medications among subgroups defined by access to nephrology care.

Literature review

The search algorithm yielded 1,865 potentially relevant original papers, of which eight articles describing frequencies of assessment of proteinuria, lipid or bone and mineral metabolism [6–10, 16, 21, 22] and 28 publications with data on ACEi or ARBs use met selection criteria [6, 8, 10, 16, 23–46]. Tables 2 and 3 summarize relevant design features and frequencies of interest of each study.

The vast majority of published studies on CKD evaluation and monitoring (Table 2) were conducted in the United States. Criteria defining kidney impairment were variable, including measured creatinine clearance, CKD staging from prediction equations, threshold serum creatinine levels and/or albuminuria. Outcome ascertainment periods also varied, where specified, from a single clinical encounter to 4 years. Reported frequencies of testing for parameters of bone and mineral metabolism ranged from 3.4 to 15% for iPTH, 29–70% for phosphorus, and 34–95% for calcium. Lipid assessment (not necessarily fractionated) was performed among 47–71% of the CKD samples, while urinary protein was quantified in 4–70%. Among studies with homogeneous ascertainment periods, testing frequencies for phosphorus and calcium were higher in more recent investigations [9, 10, 16]. Moreover, there were patterns suggesting more frequent testing among patients in nephrology practices compared to primary care or other specialties.

Table 1 Adjusted correlates of guideline-consistent monitoring by multivariable logistic regression (Odds ratio (95% confidence interval))

	Quantified urinary protein	iPTH	Serum phosphate	Serum calcium	Serum lipids
Clinical factor					
Age (per decade)	0.9 (0.7–1.3)	1.3 (0.5–2.8)	0.9 (0.5–1.4)	1.0 (0.8–1.3)	1.0 (0.8–1.2)
Male gender	0.9 (0.5–1.7)	1.3 (0.2–6.6)	1.7 (0.7–4.4)	2.0 (1.1–3.4)*	1.2 (0.8–1.7)
HTN	4.1 (1.6–10.2)†	0.9 (0.1–5.8)	2.0 (0.6–6.1)	4.5 (2.6–7.9)‡	2.9 (2.0–4.4)‡
Diabetes mellitus	7.9 (4.2–14.9)‡	0.5 (0.1–4.9)	0.6 (0.2–1.9)	18.6 (2.5–137.4)†	2.6 (1.5–4.4)†
Nephrology referral	2.0 (0.8–4.9)	14.7 (2.4–89.3)†	26.8 (10.0–71.8)‡	5.8 (0.7–44.8)	0.5 (0.3–1.0)

Effect estimates are adjusted for all other clinical factors. An odds ratio <1.0 indicates that the clinical factor was associated with decreased likelihood of monitoring for the outcome of interest. An odds ratio >1.0 indicates that the clinical factor was associated with increased likelihood of testing for the modeled outcome

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$

Table 3 describes articles published in 2000–2006 that report the frequency of ACEi/ARB use in CKD patients. Overall prescribing prevalence ranged from 34 to 81%. There was a significant temporal pattern of higher reported prescribing prevalence among CKD patients in more recent years ($r^2 = 0.54$, $P < 0.0001$ for correlation of reported prescribing frequency with starting year of study enrollment; $r^2 = 0.54$, $P < 0.0001$ for correlation of prescribing frequency with median year of study enrollment). Among those studies describing prescribing patterns according to comorbid conditions, patterns were similar to those observed in CKD in general. Prescription frequency ranged from 40 to ≥75% in patients with diabetes, and from 47 to >80% in patients with reported cardiovascular disease [6, 16, 24–27, 34, 35, 37, 38, 43, 44].

Discussion

Clinical guidelines have been developed to increase awareness of best-known practices in CKD, including characterization of disease severity and the assessment of its complications. The public health implications of CKD management are magnified by the rising prevalence of kidney disease. In the current study, we assessed the consistency of contemporary CKD care delivery with current standards recommended by K/DOQI. Using administrative data, we documented particularly low testing rates for parameters of bone and mineral metabolism, and also observed prescription of ACEi/ARBs in <50% of our total CKD study sample. Selected test performance and the use of ACEi/ARBs were generally higher among patients referred to nephrologists, but were still less than optimal. A systematic literature review demonstrated similar practice patterns nationally and internationally.

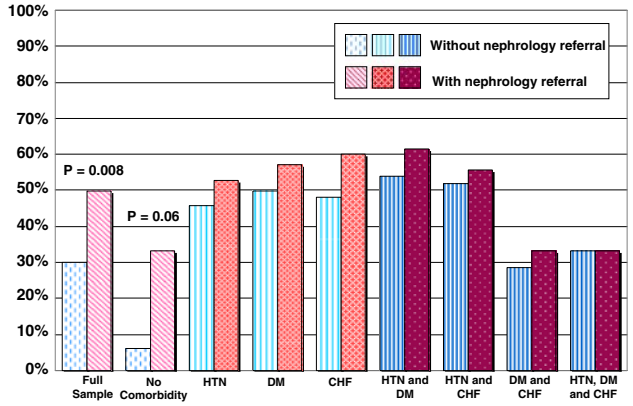

Fig. 3 Prescription of ACEi/ARBs, according to comorbidity profiles, in the study sample of patients with moderate (stage 3) CKD. *CKD* Chronic kidney disease, CHF congestive heart failure, *DM* diabetes mellitus, *HTN* hypertension

Frankly delayed referral of CKD patients to nephrologists—i.e., close to or at the time of dialysis—has been associated with suboptimal outcomes including higher mortality [12, 14]. K/DOQI guidelines recommend nephrology referral no later than when GFR decreases <30 ml/min (stage 4 CKD). While the need for nephrology referral at earlier stages of CKD is controversial [47], ideal care of CKD patients requires full awareness of treatment targets regardless of the provider specialty. Consistent with previous observations [16, 25], we found that only 8% of our study sample were referred to the nephrologists within one year of ascertaining GFR < 60 ml/min.

Compared to patients without nephrology encounters, we observed higher prevalence of testing for some parameters of bone and mineral metabolism (phosphorus and iPTH) and quantified urinary protein excretion among patients seen by nephrologists. In contrast, the frequency of assessment for dyslipidemia—a complication that has gained wide attention through National Cholesterol Education Program and Adult treatment Program III guidelines [48]—did not differ according to referral status. Lack of awareness of K/DOQI guidelines without parallels in other disease states may explain less common attention to osteodystrophy and proteinuria. In a recent survey of a national sample of American practitioners in late 2004–2005, <60% of participating family physicians correctly classified CKD stage by

Table 2 Published studies (2000–2006) reporting testing frequencies for parameters of bone and mineral metabolism, lipid metabolism and quantified proteinuria in patients with pre-dialysis chronic kidney disease

Study	Number of CKD subjects, country	Ascertainment duration and time period	Kidney function level	Data source	Referral status	Prevalence of testing within ascertainment window		
						Mineral metabolism	Lipid metabolism	Quantified urinary protein
Kausz et al. [6]	602 USA	4 years maximum; starting in 1994	S–Cr. $\geq$ 1.5 or 2.0 mg/dl	Electronic records and charts review	100% Nephrology	Calcium: 72%, Phosphorus: 69%, iPTH: 15%	Total and fractionated Cholesterol: 47 and 5%, Triglycerides: 33%	N/A
Winkelmayer et al. [7]	3014 USA	Unspecified; 1991–1996	CKD progressed to ESRD	Administrative claims	N/A	iPTH: 3.4%	N/A	N/A
Israni et al. [16]	56 USA	1 year; 1996–1999	S–Cr. $\geq$1.7 mg/dl	Charts review	100% Primary Care	Calcium: 60%, Phosphorus: 30% (if CrCl $\leq$ 50 ml/min)	N/A	19% (32% if DM)
Lafayette et al. [8]	272 USA	Single encounter; 2001–2002	S-Cr. $\geq$ 1.5 or 2.0 mg/dl	Charts review	51% Nephrology	Calcium: 76%, Phosphorus: 53% iPTH: 5%	Total or Fractionated Cholesterol: 71%	N/A
Kausz et al. [9]	24778 USA	2 years; 1998–2000	2 years before dialysis	Administrative claims	50% Nephrology	Calcium: 82%, Phosphorus: 50% iPTH:12%	Total or Fractionated Cholesterol, or Triglycerides: 58%	N/A
Murray et al. [10]	111 USA	6 months; 2001–2002	CKD stage 3–5	Charts review	100% Nephrology	Calcium: $\sim$95%, Phosphorus: 70% iPTH: 9%	Total Cholesterol: 70%	70%
de Lusignan et al. [21]	5449 UK	N/A	CKD stage 3–5 (outcomes reported only for stage 3)	Electronic clinical records	100% Primary Care	Calcium: 34%, Phosphorus: 29%	Total and fractionated cholesterol: 57 and 43%	4.2%
Stevens et al. [22]	6646 USA	1 year maximum; 2002–2003	CKD stage 1–5	Administrative claims	N/A	N/A	Lipids: 54% (type not specified)	N/A

N/A, not available; *S-Cr*, serum creatinine; *UK*, United Kingdom; *USA*, United States of America

Table 3 Details of published studies (2000–2006) reporting the prescribing frequencies for angiotensin converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers in patients with pre-dialysis chronic kidney disease

Study	Number of CKD subjects, country	Ascertainment duration and time period	Kidney function level	Data source	Referral status	ACEi/ARB prescription frequencies within ascertainment window		
						CKD study sample	CKD with DM	CKD with CVD
Hsu et al. [23]	870 USA	9 years maximum; starting in 1990	CrCl between 60–21 ml/min	Electronic clinical records	N/A	ACEi: 34%	N/A	N/A
Kausz et al. [6]	602 USA	4 years maximum; starting in 1994	S-Cr. ≥ 1.5 or 2.0 mg/dl	Electronic records and charts review	100% Nephrology	ACEi: 49%	65%	N/A
Levin et al. [24]	313 Canada	Single encounter; 1994–1997	CrCl between 75−10 ml/min	Clinical encounter	100% Nephrology	ACEi: 50%	N/A	47%
Nissenson et al. [25]	1658 USA	4 years maximum; starting in 1994	S-Cr. > 1.4 or 1.2 mg/dl	Administrative claims	22% Nephrology	ACEi: 34%*	49%*	N/A
Tonelli et al. [26, 31]	304 Canada	1 month; 1999	CrCl < 75 ml/min	Clinical encounter	100% Nephrology	ACEi/ARBs: 65%	74%	57%
London et al. [30, 32]	1936 USA	1 year; 1997–1999	1 year before dialysis onset	Administrative claims	30% Nephrology	ACEi: 38%	N/A	N/A
Khan et al. [29]	259 USA	4 years maximum; starting in 1994	S-Cr. ≥ 1.5 or 2.0 mg/dl	Electronic records and charts review	100% Nephrology	ACEi: 46%	N/A	N/A
Cleveland et al. [27]	411 Canada	Single encounter; 1998–1999	S-Cr. ≥ 1.6 or 1.2 mg/dl	Charts review	at referral to Nephrologist	ACEi/ARBs 44%	60%	N/A
De Boer et al. [28]	218 USA	2 years; Starting in 1999	CKD stage 3 to 4	Electronic records and charts review	100% Nephrology	ACEi/ARBs: 50%	N/A	N/A
Israni et al. [16]	56 USA	1 year; 1996–1999	S-Cr. ≥ 1.7 mg/dl	Charts review	100% Primary Care	ACEi/ARBs: 41%	40%	N/A
Perlman et al. [33]	620 USA	Single encounter; 2000–2002	CKD stage 3 to 5	Clinical encounter	100% Nephrology	ACEi: 53% ARBs: 22%	N/A	N/A
Lafayette et al. [8]	272 USA	Single encounter; 2001–2002	S-Cr. ≥ 1.5 or 2.0 mg/dl	Charts review	51% Nephrology	ACEi/ARBs: 58%	N/A	N/A
Ezekowitz et al. [34]	2513 Canada	At study baseline; 1995–1998	CrCl < 60 ml/min (outcomes reported only for stage 3)	Electronic clinical records	N/A	–	N/A	ACEi/ARBs: 60%
McAlister et al. [35]	625 Canada	Single encounter; in 1989–2002	CrCl < 90 ml/min (outcomes reported only for CCr < 60)	Clinical encounter	100% Cardiology	–	–	ACEi: 81%, ARBs: 4%
Rosen et al. [36]	20745 USA	1 year; 2000	Albuminuria	Administrative claims	N/A	–	ACEi/ARBs: 69%‡	N/A
So et al. [37]	1681 Hong Kong	At study baseline; 1995–2001	Albuminuria	Electronic clinical records	N/A	–	ACEi/ARBs: 75%‡	N/A

Table 3 continued

Study	Number of CKD subjects, country	Ascertainment duration and time period	Kidney function level	Data source	Referral status	ACEi/ARB prescription frequencies within ascertainment window		
						CKD study sample	CKD with DM	CKD with CVD
Murray et al. [10]	111 USA	6 months; 2001–2002	CKD stage 3 to 5	Charts review	100% Nephrology	ACEi/ARBs: 62%	N/A	N/A
Bailie et al. [38]	619 USA	Single encounter; 2000–2002	CKD stage 2 to 5	Clinical encounter	100% Nephrology	ACEi: 44% ARBs: 13%	ACEi: 58% ARBs: 23%‡	N/A
De Nicola et al. [39]	713 Italy	Single encounter; 2002–2003	CrCl < 70 ml/min	Clinical encounter	100% Nephrology	ACEi/ARBs: 70%	N/A	N/A
Leehey et al. [40]	343 USA	10 year maximum; 1993–2002	CKD stage 2 to 5	Electronic clinical records	N/A	–	ACEi/ARBs: 71%‡	N/A
Minutolo et al. [41]	445 Italy	Single encounter; 2003	CKD stage 3 to 4	Clinical encounter	42% Nephrology	ACEi/ARBs: 81%	N/A	N/A
Thanamayooran et al. [42]	304 Canada	4 years maximum; Starting in 1998	S-Cr. ≥ 1.6 or 1.2 mg/dl	Charts review	100% Nephrology	ACEi/ARBs: 64%	N/A	N/A
Winkelmayer et al. [43]	1243 USA	3 months; 2003	Albuminuria	Administrative claims	N/A	–	ACEi/ARBs: 47%‡	N/A
Jayapaul et al. [44]	130 UK	10 years; 1991–2001	Albuminuria	Electronic records and charts review	27% Nephrology 48% Diabetology	–	ACEi: 64%‡	N/A
Jones et al. [45]	949 UK	3 years; 1997–2003	CKD stage 3 to 5	Electronic clinical records	100% Nephrology	ACEi/ARBs: 52%	N/A	N/A
Parikh et al. [46]	281 USA	Single encounter; 1998–2001	CKD stage 3	Clinical encounter	N/A	ACEi: 37%	–	–

CrCl, creatinine clearance; *CVD*, cardiovascular disease

* Annualized percentage

‡ Data refer to diabetic patients with proteinuria

estimated GFR; 87% failed to recommend testing for iPTH in a hypothetical patient with stage 3–4 CKD and 59% did not recommend phosphorus measurement [49]. Further, approximately 66% of primary care physicians in this survey were unaware of clinical practice guidelines for CKD, and 45% did not believe that medical care slows CKD progression. Of note, the frequency of urinary protein quantification increased significantly over time among patients without nephrology referral in our administrative sample, suggesting the possibility of some guideline dissemination to non-specialists even during the short timeframe of the study.

In our study sample and the reviewed literature, calcium was the most frequently ordered parameter of bone and mineral metabolism. The utility of calcium levels in evaluating clinical conditions other than osteodystrophy may explain its more routine measurement. In addition, calcium is included in the most commonly ordered metabolic panels ("basic metabolic" and "comprehensive metabolic" panels) in the United States, whereas phosphorus in packaged only in the "renal" panel (which also includes calcium) and measurement of iPTH requires separate requisition. Thus, more prevalent calcium assessments may also reflect the packaging of this test within routine panels.

Medications that block the rennin–angiotensin–aldosterone cascade may slow CKD progression, and appear particularly important in proteinuric kidney diseases such as diabetic nephropathy. ACEi/ARBs also reduce cardiovascular morbidity and are a cornerstone of contemporary heart failure therapy. We observed significant, 70% relative increased prevalence of overall ACEi/ARBs use among CKD patients with versus without nephrology referral. This difference appeared in part mediated by the higher burden of relevant comorbidities among referred patients. Within comorbidity-stratified sub-samples, we observed non-significant trends towards only slightly higher prescribing of ACEi/ARBs among patients referred to nephrologists; there was also a nearly significant ($P = 0.06$) trend towards more frequent use of ACEi/ARBs in CKD patients without other identified comorbidities seen by nephrologists. Given the small numbers of nephrology-referred patients within the stratified sub-samples, we did not have adequate statistical power to determine if these modest differences reflected true differences in practice patterns. Nonetheless, the fact that stratification by comorbidity attenuated much of the observed difference in overall ACEi/ARB use according to referral status among CKD patients suggests that some prescribing is directed more to the management of other conditions rather than to the awareness of CKD per se. In support of this hypothesis, while 80% of participants in a recent survey of American primary care physicians expressed reliance on guidelines issued for diabetes and hypertension (ADA and JNC VI), only 20% expressed reliance on K/DOQI [50].

Our observation of use of ACEi/ARBs in 50% of CKD patients seen by kidney disease specialists is similar to many published reports [6, 8, 10, 16, 24, 27–29, 38, 45]. Although we did not detect a temporal pattern of increasing use of ACEi/ARBs within the relatively short timeframe of the administrative analysis, our literature review suggested a linear trend of increasing reported use of these medications among CKD patients over a broader observation period spanning 1990–2003 [31, 33, 39, 42]. Concern for side effects may explain lack of administration to some CKD patients. The only absolute contraindication for ACE/ARB prescription is angioedema, which has been estimated to occur in <1% of treated patients [51]. Observational data suggest that metabolic complications of hyperkalemia and renal functional deterioration affect approximately 12–19% of CKD patients receiving ACEi/ARB, although these estimates derive from patients with stage 4–5 disease, who are more vulnerable than stage 3 patients to metabolic imbalances [8, 16, 31, 37]. Further, hyperkalemia and unacceptable deterioration in GFR are generally reversible with medication cessation. Overall, expected complication rates are not high enough to account for apparent underprescribing in patients who may benefit from ACEi/ARBs.

Administrative claims are emerging as a useful data source for characterization of the care patterns and outcomes of patients with chronic illness [52–54]. Although billing claims may have suboptimal sensitivity for identification of diagnoses due to under-coding [22], claims have been shown to be highly sensitive and specific for delivered services such as tests and pharmacy prescriptions, effectually serving as receipts for service [55]. Ascertainment of calcium testing in a high fraction of the study sample (including nearly all patients seen by nephrologists) supports good capture of claims for the study participants and implicates provider decision-making as the reason for lower rates of other outcomes of interest.

Our study is limited by the use of a single serum creatinine level for CKD classification. We attempted to minimize risk of misclassifying patients with acute renal injury as having CKD by sampling based only on ambulatory rather than inpatient creatinine levels, as done by others [53]. Another source of possible misclassification is the lack of information on participant race. As the aMDRD equation includes a scaling factor of 1.21 for black race, GFR was underestimated for African-American participants by approximately 21%. However, as African–Americans account for only 11% of the population of the sampled states and the United States Census Bureau reports that 50% or fewer of black Americans are privately insured [56], potential misclassification of CKD based on race likely affected only a small number of participants. Use of data describing healthcare beneficiaries in a particular geographic region may limit the generalizability of our

findings. For this reason we framed our results in the context of a literature review and found similar reported practice patterns in the United States and other countries.

This investigation of focus areas of CKD care delivery, as captured by administrative data and a systematic literature review, describes contemporary clinical practice in relation to a benchmark of practice guidelines. We observed a particularly high prevalence of recommended dyslipidemia assessment, a measure that overlaps practice guidelines for more general populations. In contrast, although nephrologists appear more attentive to CKD-specific recommendations such as measurement of proteinuria and parameters of mineral metabolism, there is opportunity for improvement even in care delivered by kidney specialists. Further attention should be given to strategies to increase optimal care in CKD regardless of provider specialty.

Acknowledgments Ms. Buchanan received support from a Public Policy Fellowship from the American Society of Transplantation. Dr. Brennan received support from a grant from the National Institute of Diabetes Digestive and Kidney Diseases (NIDDK), K24-DK002886. Dr. Lentine received support from a grant from the NIDDK, K08-DK073036. An abstract describing a portion of this work was presented at the American Society of Nephrology 39th Annual Renal Week Meeting on November 18, 2006, in San Diego, CA, USA.

Appendix 1

Table 4

Table 4 Common procedural terminology (CPT) codes used to identify recommended testing of parameters of bone and mineral metabolism, serum lipids and quantified urinary protein according to K/DOQI guidelines

Clinical measure	K/DOQI guideline for testing frequency	Test/panel	CPT code
Serum iPTH	Annually	Intact PTH	83970
Serum phosphorus	Annually	Phosphate	84100
		Renal Panel	80069
Serum calcium	Annually	Calcium	82310
		Basic metabolic panel	80048
		Comprehensive metabolic panel	80053
		Renal panel	80069
Serum lipids	Annually	Lipid panel	80061
Quantified proteinuria	At Diagnosis Scored as adherent if recorded within 1 year of index	Albumin, urine, quantitative	82042
		Albumin, urine, microalbumin, quant.	82043
		Albumin, urine, microalbumin, semi-quant.	82044
		Assay of protein, urine	84156

Appendix 2

Table 5

Table 5 List of medical subject heading (MeSH) terms used to perform a systematic review of the literature published from 2000 to 2006 about the delivery of care relating to proteinuria quantification, bone and lipid metabolism assessment and ACEi/ARBs prescription in CKD

MeSH terms	
CKD and pre dialysis care	"Kidney failure, chronic", "Kidney diseases", "Nephrology", "Primary health care", "Family practice", "Ambulatory care"
Care delivery assessment	"Outcome and process assessment (Health Care)", "Guideline adherence", "Practice guidelines", "Diagnostic tests, routine"
Bone and mineral metabolism	"Metabolic diseases", "Bone diseases", "Hyperparathyroidism, secondary", "Parathyroid hormone", "Phosphorus", "Calcium"
Proteinuria	"Proteinuria", "Diabetes complications"
Lipid metabolism	"Dyslipidemias", "Hyperlipidemias", "Hypercholesterolemia", "Lipids", "Cholesterol", "Cholesterol, HDL", "Cholesterol, LDL", "Triglycerides"
ACEi/ARBs use	"Hypertension/complications/diagnosis/epidemiology/prevention & control", "Cardiovascular diseases/complications/diagnosis/epidemiology/etiology/prevention & control", "Cardiovascular agents/therapeutic use", "Angiotensin-converting enzyme inhibitors/therapeutic use", "Angiotensin II Type 1 Receptor Blockers", "Drug utilization/statistics and numerical data/classification/trends", "Blood pressure/drug effects", "Hypertension/therapy/drug therapy"

References

1. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003;41(1):1–12.
2. Healthy People 2010 obtained from http://www.healthypeople.gov/about/hpfact.htm.
3. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. Ann Inter Med. 2005;142(5):342–51.
4. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet. 1999;354(9176):359–64.
5. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Inter Med. 2003;139(4):244–52.
6. Kausz AT, Khan SS, Abichandani R, Kazmi WH, Obrador GT, Ruthazer R, et al. Management of patients with chronic renal

insufficiency in the Northeastern United States. J Am Soc Nephrol. 2001;12(7):1501–7.
7. Winkelmayer WC, Levin R, Avorn J. The nephrologist's role in the management of calcium-phosphorus metabolism in patients with chronic kidney disease. Kidney Int. 2003;63(5):1836–42.
8. Lafayette RA, Lai G. Examining chronic kidney disease management in a single center. Clin Nephrol. 2004;62(4):260–6.
9. Kausz AT, Guo H, Pereira BJ, Collins AJ, Gilbertson DT. General medical care among patients with chronic kidney disease: opportunities for improving outcomes. J Am Soc Nephrol. 2005;16(10):3092–101.
10. Murray BM, Malireddi K, Vavilala V. Delivery of predialysis care in an academic referral nephrology practice. Ren Fail. 2005;27(5):571–80.
11. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1–266.
12. Avorn J, Bohn RL, Levy E, Levin R, Owen WF Jr, Winkelmayer WC, et al. Nephrologist care and mortality in patients with chronic renal insufficiency. Arch Inter Med. 2002;162(17):2002–6.
13. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag MJ, Levey AS, et al. The timing of specialist evaluation in chronic kidney disease and mortality. Ann Inter Med. 2002;137(6):479–86.
14. Obrador GT, Pereira BJ. Early referral to the nephrologist and timely initiation of renal replacement therapy: a paradigm shift in the management of patients with chronic renal failure. Am J Kidney Dis. 1998;31(3):398–417.
15. De Nicola L, Minutolo R, Chiodini P, Zoccali C, Castellino P, Donadio C, et al. Global approach to cardiovascular risk in chronic kidney disease: reality and opportunities for intervention. Kidney Int. 2006;69(3):538–45.
16. Israni A, Korzelius C, Townsend R, Mesler D. Management of chronic kidney disease in an academic primary care clinic. Am J Nephrol. 2003;23(1):47–54.
17. Lenz O, Mekala DP, Patel DV, Fornini A, Metz D, Roth D. Barriers to successful care for chronic kidney disease. BMC Nephrology. 2005;6:11.
18. Saelen MG, Prosch LK, Gudmundsdottir H, Dyrbekk D, Helge Hunderi O, Arnesen E, et al. Controlling systolic blood pressure is difficult in patients with diabetic kidney disease exhibiting moderate-to-severe reductions in renal function. Blood Press. 2005;14(3):170–6.
19. National Kidney F. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003;42(4 Suppl 3):S1–201.
20. Kidney Disease Outcomes Quality Initiative G. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis. 2003;41(4 Suppl 3):I–IV.
21. de Lusignan S, Chan T, Stevens P, O'Donoghue D, Hague N, Dzregah B, et al. Identifying patients with chronic kidney disease from general practice computer records. Fam Pract. 2005;22(3):234–41.
22. Stevens LA, Fares G, Fleming J, Martin D, Murthy K, Qiu J, et al. Low rates of testing and diagnostic codes usage in a commercial clinical laboratory: evidence for lack of physician awareness of chronic kidney disease. J Am Soc Nephrol. 2005;16(8):2439–48.
23. Hsu CY, Bates DW, Kuperman GJ, Curhan GC. Blood pressure and angiotensin converting enzyme inhibitor use in hypertensive patients with chronic renal insufficiency. (see comment). Am J Hypertens. 2001;14(12):1219–25.
24. Levin A, Djurdjev O, Barrett B, Burgess E, Carlisle E, Ethier J, et al. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. Am J Kidney Dis. 2001;38(6):1398–407.
25. Nissenson AR, Collins AJ, Hurley J, Petersen H, Pereira BJ, Steinberg EP. Opportunities for improving the care of patients with chronic renal insufficiency: current practice patterns. J Am Soc Nephrol. 2001;12(8):1713–20.
26. Tonelli M, Bohm C, Pandeya S, Gill J, Levin A, Kiberd BA. Cardiac risk factors and the use of cardioprotective medications in patients with chronic renal insufficiency. Am J Kidney Dis. 2001;37(3):484–9.
27. Cleveland DR, Jindal KK, Hirsch DJ, Kiberd BA. Quality of prereferral care in patients with chronic renal insufficiency. Am J Kidney Dis. 2002;40(1):30–6.
28. De Boer IH, Gorodetskaya I, Young B, Hsu CY, Chertow GM. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol. 2002;13(11):2762–9.
29. Khan SS, Kazmi WH, Abichandani R, Tighiouart H, Pereira BJ, Kausz AT. Health care utilization among patients with chronic kidney disease. Kidney Int. 2002;62(1):229–36.
30. London R, Solis A, Goldberg GA, Wade S, Ryu S. Health care resource utilization and the impact of anemia management in patients with chronic kidney disease. Am J Kidney Dis. 2002;40(3):539–48.
31. Tonelli M, Gill J, Pandeya S, Bohm C, Levin A, Kiberd BA. Barriers to blood pressure control and angiotensin enzyme inhibitor use in Canadian patients with chronic renal insufficiency. Nephrol Dial Transplant. 2002;17(8):1426–33.
32. London R, Solis A, Goldberg GA, Wade S, Chan WW. Examination of resource use and clinical interventions associated with chronic kidney disease in a managed care population. J Manage Care Pharm. 2003;9(3):248–55.
33. Perlman RL, Kiser M, Finkelstein F, Eisele G, Roys E, Liu L, et al. The longitudinal chronic kidney disease study: a prospective cohort study of predialysis renal failure. Semin Dial. 2003;16(6):418–23.
34. Ezekowitz J, McAlister FA, Humphries KH, Norris CM, Tonelli M, Ghali WA, et al. The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. J Am College Cardiol. 2004;44(8):1587–92.
35. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. (see comment). Circulation. 2004;109(8):1004–9.
36. Rosen AB, Karter AJ, Liu JY, Selby JV, Schneider EC. Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in high-risk clinical and ethnic groups with diabetes. J Gen Inter Med. 2004;19(6):669–75.
37. So WY, Ozaki R, Chan NN, Tong PC, Ho CS, Lam CW, et al. Effect of angiotensin-converting enzyme inhibition on survival in 3773 Chinese type 2 diabetic patients. Hypertension. 2004;44(3):294–9.
38. Bailie GR, Eisele G, Liu L, Roys E, Kiser M, Finkelstein F, et al. Patterns of medication use in the RRI-CKD study: focus on medications with cardiovascular effects. Nephrol Dial Transplant. 2005;20(6):1110–5.
39. De Nicola L, Minutolo R, Zamboli P, Cestaro R, Marzano L, Giannattasio P, et al. Italian audit on therapy of hypertension in chronic kidney disease: the TABLE-CKD study. Semin Nephrol. 2005;25(6):425–30.
40. Leehey DJ, Kramer HJ, Daoud TM, Chatha MP, Isreb MA. Progression of kidney disease in type 2 diabetes—beyond blood pressure control: an observational study. BMC Nephrol. 2005;6(1):8.
41. Minutolo R, De Nicola L, Zamboli P, Chiodini P, Signoriello G, Toderico C, et al. Management of hypertension in patients with

CKD: differences between primary and tertiary care settings. Am J Kidney Dis. 2005;46(1):18–25.
42. Thanamayooran S, Rose C, Hirsch DJ. Effectiveness of a multidisciplinary kidney disease clinic in achieving treatment guideline targets. Nephrol Dial Transplant. 2005;20(11):2385–93.
43. Winkelmayer WC, Fischer MA, Schneeweiss S, Wang PS, Levin R, Avorn J. Underuse of ACE inhibitors and angiotensin II receptor blockers in elderly patients with diabetes. Am J Kidney Dis. 2005;46(6):1080–7.
44. Jayapaul MK, Messersmith R, Bennett-Jones DN, Mead PA, Large DM. The joint diabetic-renal clinic in clinical practice: 10 years of data from a District General Hospital. Qjm. 2006;99(3):153–60.
45. Jones C, Roderick P, Harris S, Rogerson M. An evaluation of a shared primary and secondary care nephrology service for managing patients with moderate to advanced CKD. Am J Kidney Dis. 2006;47(1):103–14.
46. Parikh NI, Hwang SJ, Larson MG, Meigs JB, Levy D, Fox CS. Cardiovascular disease risk factors in chronic kidney disease: overall burden and rates of treatment and control. Arch Inter Med. 2006;166(17):1884–91.
47. Jones C, Roderick P, Harris S, Rogerson M. Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease. Nephrol Dial Transplant. 2006;21:2133–43.
48. National Cholesterol Education Program (NCEP) and Adult treatment Program III (ATP III) guidelines available at http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.
49. Boulware LE, Troll MU, Jaar BG, Myers DI, Powe NR. Identification, referral of patients with progressive CKD: a national study. Am J Kidney Dis. 2006;48(2):192–204.
50. Lea JP, McClellan WM, Melcher C, Gladstone E, Hostetter T. CKD risk factors reported by primary care physicians: do guidelines make a difference? Am J Kidney Dis. 2006;47(1):72–7.
51. Kostis JB, Kim HJ, Rusnak J, Casale T, Kaplan A, Corren J, et al. Incidence and characteristics of angioedema associated with enalapril. Arch Inter Med. 2005;165(14):1637–42.
52. Gilmer TP, O'Connor PJ, Rush WA, Crain AL, Whitebird RR, Hanson AM, et al. Predictors of health care costs in adults with diabetes. Diabetes Care. 2005;28(1):59–64.
53. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. New Engl J Med. 2004;351(13):1296–305.
54. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Inter Med. 2002;162(20):2269–76.
55. Stirnemann PM, Takemoto SK, Schnitzler MA, Brennan DC, Abbott KC, Salvalaggio P, et al. Agreement of immunosuppression regimens described in Medicare pharmacy claims with the Organ Procurement and Transplantation Network survey. J Am Soc Nephrol. 2006;17(8):2299–306.
56. Income, Poverty, and Health Insurance Coverage in the United States:2005. Obtained from US Census Bureau website (http://www.census.gov).