Challenges and opportunities in late-stage chronic kidney disease*

Steven Fishbane, Azzour D. Hazzan, Candice Halinski and Anna T. Mathew

Department of Medicine, Division of Nephrology, Hofstra North Shore LIJ School of Medicine, Great Neck, NY, USA

Correspondence to: Steven Fishbane; E-mail: sfishbane@nshs.edu

Abstract
There is increasing recognition that chronic diseases are a major challenge for health delivery systems and treasuries. These are highly prevalent and costly diseases and frequency is expected to increase greatly as the population of many countries ages. Chronic kidney disease (CKD) has not received the same attention as other chronic diseases such as congestive heart failure; yet, the prevalence and costs of CKD are substantial. Greater recognition and support for CKD may require that the disease no longer be viewed as one continuous disease state. Early CKD stages require less complex care and generate lower costs. In contrast, late-stage CKD is every bit as complex and costly as other major chronic diseases. Health authorities may not recognize and fund CKD care appropriately until late-stage CKD is defined clearly as separate and distinct from earlier stages of disease. In this review, we describe the burden of chronic diseases, consider the challenges and barriers and propose processes to improve late-stage CKD care. In particular, we recommend the need for improved continuity of care, enhanced use of information technology, multidisciplinary care, timely referral to nephrologists, protocol use and improved patient engagement.

Keywords: care management; CKD; health systems; late-stage CKD

Global burden of chronic disease

The burden of chronic disease has a wide reach, affecting individuals and health systems in low-, middle- and high-income countries. The Global Non-Communicable Disease (NCD) Action Plan, endorsed by the World Health Assembly in 2008, identified cardiovascular disease, cancer, respiratory disease and diabetes as priority diseases since they represent the bulk of NCDs and their development can be attributed to risk behaviors which may be modifiable through public health action (e.g. tobacco smoking, lack of physical activity and unhealthy diet) [1]. As of 2012, half of all adult Americans have one or more chronic health conditions [2]. The prevalence of diabetes approaches 11% in many countries, and 12.7 million new cases of cancer were diagnosed in 2008 worldwide [3]. Globally, chronic NCDs are the most common cause of death and morbidity. In 2008, 63% of all deaths worldwide (36 of 57 million) were due to chronic disease, and this risk is projected to increase by 15% between 2010 and 2020 [4]. Diabetes is a leading cause of blindness, renal failure and limb amputation in many countries [5, 6], and the number of stroke survivors worldwide is estimated to reach 77 million by 2030 [7]. Without a coordinated prevention and management plan, health systems across the globe are now faced with the ‘neglected epidemic of chronic disease’ [8].

The economic consequences of this burgeoning epidemic are massive, with impact on both individuals and health systems. At the household and individual level, chronic disease and poverty are inextricably linked. Low-income men and women are at higher risk for chronic disease, while the high cost of health care in many countries leads to loss of household income. Each year, 100 million people are pushed below the poverty line due to out-of-pocket health-care costs [9]. At the national level, in 2010 the USA spent $315 billion on cardiovascular disease [10] and $157 billion on cancer care [11]. Chronic diseases account for 84% of all health care spending in the USA [12]. Estimated losses to national income from cardiovascular disease and diabetes in 2005 were US $18 billion in China, and $9 billion in India [13]. As a result, in 2010 the World Economic Forum placed chronic diseases among the most consequential and severe threats to economic development [14].

Contrary to conventional thinking, the adverse consequences of chronic disease are not an exclusive problem of high-income nations. In sub-Saharan Africa, the prevalence of cardiovascular disease and type 2 diabetes has...
increased 10-fold from 1980 to 2008 [15]. Globally, 80% of all deaths from chronic disease now occur in low- and middle-income countries [16]. This rapid rise in resource-poor nations places a burden on fragile health systems.

Although not identified directly as a priority disease under the Global NCD Action Plan, chronic kidney disease (CKD) has a complex and reciprocal relationship with other chronic diseases. Worldwide, hypertension and diabetes are the leading causes of CKD, and these diseases share common, modifiable risk factors for development. CKD is a major risk factor for development of cardiovascular disease [17], and also increases the risk of cardiovascular mortality by 8- to 10-fold [18, 19]. Currently, the prevalence of moderate to severe CKD (Stages 3–5) ranges from 5 to 7% in most countries [20, 21], and as the prevalence of diabetes, hypertension and cardiovascular disease is projected to rise, so will the global burden of CKD. In addition, low-income status is also disproportionately associated with CKD, with increased risk of albuminuria, progression of CKD and end-stage renal disease (ESRD) [22–24].

Once ESRD develops, the clinical and economic burden of disease is dramatically increased. Worldwide, ~2 million people currently require renal replacement therapy (RRT) for ESRD [25]. Developed countries spend ~1% of their entire national health-care budget on treatment for ESRD [26]. Several developing countries do not have the resources to provide any form of RRT. As a consequence, 1 million people die from untreated ESRD each year [27]. Overall mortality in ESRD patients on RRT is 10–100 times higher than age-matched controls with normal renal function [28]. Evidence-based management strategies have been well demonstrated to slow the progression of CKD [29, 30]. Unfortunately, awareness of disease in CKD patients remains low (often <20%) [31], and remains an important barrier to accessing care.

Late-stage CKD and barriers to optimal outcomes

The great burden imposed by chronic diseases on the treasury and health-care systems of industrialized countries leads to an important, but perhaps overly focused concentration on congestive heart failure (CHF) and related diseases and less attention on the importance of CKD. Yet, CKD affects a large number of patients and has a great impact on health outcomes, quality-of-life experience and total cost of health care. In 2011, CKD was present in 9.2% of US Medicare beneficiaries and accounted for 18.2% of their entire national health-care budget on treatment for ESRD [26]. Developed countries spend 2–3% of their national health-care budget on treatment for ESRD [26]. Several developing countries do not have the resources to provide any form of RRT. As a consequence, 1 million people die from untreated ESRD each year [27]. Overall mortality in ESRD patients on RRT is 10–100 times higher than age-matched controls with normal renal function [28]. Evidence-based management strategies have been well demonstrated to slow the progression of CKD [29, 30]. Unfortunately, awareness of disease in CKD patients remains low (often <20%) [31], and remains an important barrier to accessing care.

### Late-stage CKD and barriers to optimal outcomes

The great burden imposed by chronic diseases on the treasury and health-care systems of industrialized countries leads to an important, but perhaps overly focused concentration on congestive heart failure (CHF) and related diseases and less attention on the importance of CKD. Yet, CKD affects a large number of patients and has a great impact on health outcomes, quality-of-life experience and total cost of health care. In 2011, CKD was present in 9.2% of US Medicare beneficiaries and accounted for 18.2% of costs [32]. From 2000 to 2011, while the total expenditures of the Medicare system increased by ~100%, the Medicare costs for CKD increased by 380% [32]. The USA, in its Healthy People 2020 campaign, is seeking to ‘reduce new cases of chronic kidney disease (CKD) and its complications, disability, death, and economic costs’ [32]. A similar focus is in place in many other industrialized nations.

Public health success in CKD management may be hampered by the prevailing view of CKD as one continuous disease state, albeit with several stages. In fact, early-stage CKD (Stages 1–3) is so qualitatively different than late-stage CKD that a disservice is done by considering CKD as a single disease state. Early-stage CKD is marked by far less complexity than later stage disease, fewer nephrologist office visits and less of an impact on health and economic outcomes. As an example, the cost of care for both younger and older patients with CKD remains somewhat constant for Stages 1–3 [32]. In late-stage CKD (Stages 4–5), the focus of care shifts from preventing disease progression to dialysis modality selection, preparation for ESRD and managing the complications of kidney disease. The complexity of interacting diseases and degradation of quality of life imposed by late-stage CKD makes it a disease entity that is qualitatively and quantitatively different than early-stage CKD. Outcomes in late-stage CKD are generally suboptimal; reflected by the high rates of hospitalization [33] and mortality [34], low rates of home dialysis selection and pre-emptive transplantation, and nearly 80% of patients initiate hemodialysis with a catheter [32]. Indeed, late-stage CKD has much in common with other chronic diseases such as CHF, advanced COPD and diabetes. Public health authorities may find it hard to view all of CKD with its inherent heterogeneity as important enough to prioritize in parallel with CHF and advanced COPD. In contrast, late-stage CKD clearly is worthy of prioritization and allocation of resources.

In the following section, we will review important barriers imposed by the current model of health care, which affect the care of patients with late-stage CKD. These barriers arise out of an outdated model of medical management that is well suited to treatment of acute medical problems and health maintenance but poorly matched to the needs of patients with severe chronic conditions such as late-stage CKD.

### Barriers to optimal care in late-stage CKD

#### Delayed referral to nephrologists

For many patients with CKD, referral to the nephrologist is delayed until RRT initiation (Table 1 and Figure 1). Although no definitive guideline exists to recommend when referral should occur, at least a 12-month period prior to RRT provides most patients and nephrologists an adequate window to optimize medical management, while educating and preparing the patient for RRT. Despite this, in 2011, 73.7% of incident dialysis patients either had never seen a nephrologist (42.1%) or had seen one for <12 months (31.6%). These patients can have severe complications accompanying late-stage CKD including anemia, mineral and bone disease and volume overload, making their initiation of RRT complex and prone to poor outcomes. While there are many determinants of delayed referral, older patient age and predominant care by an internist (versus primary care practitioner) have been described [35]. Nephrologist care prior to starting hemodialysis reduces catheter use at Day 1 of dialysis, but 65% of patients treated by a nephrologist in the USA for more than 12 months still started dialysis with a catheter in place [32]. Hence, even with timely referral to the nephrologist, patient outcomes can still be improved, demonstrating that multiple barriers can contribute to suboptimal care in late-stage CKD.

#### Episodic outpatient care

In late-stage CKD, most patients see their nephrologist every 1–3 months. This may not be sufficient as there are

| Table 1. Barriers to optimal late-stage CKD care |
|------------------------------------------------|
| Delayed referral to nephrologists |
| Episodic outpatient care |
| Fragmentation of care |
| Inadequate patient education |
| Poor communication |
many adverse events that can occur between nephrologist appointments. Volume status can fluctuate, due to dietary indiscretions or changes in medication, and can result in hospitalization [36]. A busy outpatient office does not lend itself to the ongoing patient education required to facilitate dialysis modality choice. Intermittent and brief discussions of vascular access placement can result in failure to secure a matured fistula prior to RRT initiation; a situation all too familiar to many nephrologists. The current medical model of episodic nephrologist office visits is not well matched to the needs of the late-stage CKD; these patients are complex and require bridging care between office visits to optimize medical conditions, prevent complications, facilitate care plan progress and strengthen patient education and self-management.

**Fragmentation of care**

Patients with late-stage CKD often have complex medical issues and other concomitant chronic diseases that require attention from several specialists, along with a primary care physician. The web of multiple physicians often results in fragmentation that arises from inadequate communication and failure to develop an established, unified care plan. Recommendations from the patient’s nephrologist may conflict with other specialists, and vice versa [37]. Physicians without expertise in nephrology may add new medications that are potentially unsafe in advanced kidney disease. In Italy, it was recently found that up to 50% of CKD patients were prescribed an inappropriate drug [38]. A classic example of fragmentation is the ‘dance’ between nephrologists and cardiologists. Cardiology evaluation reveals dyspnea and the diuretic dose is increased. Weeks later, the nephrologist sees the patient and notes that the serum creatinine has increased. The diuretic dose is withheld and perhaps the angiotensin blocking agent is held as well. Without adequate communication and coordination between both specialists, the risk for hospitalization for decompensated congestive heart failure or acute kidney injury may occur. While multiple care providers are requisite for the complex patient with late-stage CKD, the current health-care model often results in medical care that is contradictory, rather than complementary.

**Fig. 1.** The prevailing care model in late-stage CKD results in several barriers to achieving optimal outcomes. We propose pathways to improvement that create a true collaborative care model.
Late-stage kidney disease

Inadequate patient education

Lack of disease state education results in patients ill equipped to cope with the critical decisions imposed by late-stage CKD and leaves patients prone to complications of the disease. Educational needs extend broadly in late-stage kidney disease [39]. Understanding of kidney disease itself is important to motivate compliance and patient activation. Diet education is an important non-pharmacological therapy that facilitates patient self-management; however, patients can become frustrated with conflicting diet instructions prescribed by different specialists. For patients to make an informed choice of dialysis modality, education plays a key role. Insufficient education results in patients in many industrialized countries ‘choosing’ in-center hemodialysis mostly by default [40]. Despite this, a recent survey of US dialysis patients reported one-third of dialysis patients received little or no education regarding dialysis modality [41]. Globally, education of patients with kidney disease may be improving. A recent European Kidney Patients’ Federation (CEAPiR) survey found that most patients felt a reasonable level of satisfaction with education provided [42].

Poor communication

Several of the barriers discussed above are exacerbated by poor communication between patient and physician, or between physicians. For example physician to patient communication often breaks down in the context of modality selection, thus impeding patient education. Patients may resist the idea that a minimally symptomatic disease (at present) will result in the need for a treatment as drastic as dialysis in the near future. Cultural or religious beliefs may give a false sense of security. The burden of multiple comorbid conditions and the medicalization that occurs when one’s life is dominated by physician appointments may make it difficult to accept the addition of yet another burden in dialysis treatment. Depression and anxiety certainly play a central role as well [43].

Poor communication about modality selection can also be related to nephrologist hesitancy. A physician’s desire to avoid conflict and a reluctance to accept treatment ‘failure’ contributes to this hesitancy. Substantive modality education cannot begin until these patient and nephrologist factors are addressed. Poor communication between several physicians caring for a complex late-stage CKD patient worsens fragmentation of care. Conflicting medical opinions can frustrate the patient, lead to unnecessary delays in care, duplication of testing and even harm to the patient if medications are being managed by several physicians independently.

Thus far, we have outlined the global burden of chronic disease including CKD, described how the current model of medical management may be poorly suited to patients with chronic conditions and listed barriers to optimal outcomes in patients with late-stage CKD. Changes to the care delivery model could improve outcomes in these patients including increased pre-emptive transplantation, home dialysis initiation, reduction in dialysis catheter use, patient quality of life, hospitalization and mortality. We propose an approach involving six tenets to specifically address the failures of the current care model and subsequent barriers to optimal outcomes. These six tenets include (i) continuity of care, (ii) enhanced use of information technology, (iii) multidisciplinary care, (iv) timely referral to a nephrologist, (v) protocol use and (vi) patient engagement. We will provide examples of how we have implemented these approaches in a late-stage CKD program at our institution, Healthy Transitions (HT) in Late-Stage CKD. We will next briefly describe the HT program and then review our six proposed tenets of care.

Healthy transitions in late-stage CKD program

At our academic institution, we instituted a late-stage CKD program in October, 2012. Healthy Transitions is a collaborative care management model. The two most important components are a nurse care manager program and a relational database informatics system. The HT program was designed to meet the demands of late-stage CKD patients through evidenced-based education, care coordination, program protocols, innovative information/technology and supportive services for patient self-management. To date, the HT program has reduced hospitalizations, realized a 12.1% pre-emptive transplant rate, a 68.1% functioning AV fistula rate at Day 1 of dialysis and only a 22.7% total catheter rate at initiation. Forty-one percent of patients started dialysis without a hospitalization and 32.4% patients started on peritoneal dialysis. As we discuss overcoming barriers to care, we will intersperse information derived from the HT program experience.

Six tenets to overcome barriers and improve outcomes in late-stage CKD

Continuity of care

In the previous section, we discussed how the current care model is out of step with the needs of patients with chronic diseases. One barrier, the episodic nature of nephrologist office visits may leave the late-stage CKD patient exposed between visits because there are so many medical events, care processes that need to be achieved, medication changes and other physician visits with changes in treatment. In CHF, the problem of episodic care (or how to manage the interappointment period) has been addressed with both high-tech and lower tech solutions. Implantable monitors help cardiologists monitor volume status continuously. In the HT program, we have utilized daily weight monitoring with computerized analysis of patterns to help prevent volume overload admissions, which are common in late-stage CKD. Ultimately, the most powerful bridge between nephrologist visits in the HT program is a combination of low and high tech. It is nurse care managers guided by a sophisticated informatics system that help to monitor patients, provide education and ensure that care plans are progressing between appointments. In chronic disease, greater continuity of care has demonstrable benefit, a 50% reduction in hospital readmissions in CHF [43], reduced symptomatology in COPD [44] and our HT program’s reduction in hospitalizations and other improved outcomes in late-stage CKD.

Enhanced use of information technology

Electronic medical records. The current system where high-risk patients often move between different clinics and subspecialties is prone to fail unless providers take an active role in communicating with each other. An electronic medical record (EMR) can greatly facilitate communication.
Medical informatics. In the HT program, we use informatics to link patient data to clinical protocols and to generate alerts to the nurse care managers (Figure 2). Every morning, the nurse receives a report listing his/her full roster of patients. Alerts are generated for a variety of problems including delayed modality selection, acute weight changes, medication discrepancies and incomplete advance directives. The alerts become very specific for critical pathway steps related to optimal care processes. For example for patients who have chosen hemodialysis as a modality, alerts guide the nurse to facilitate sequential process steps for AVF placement; making a surgical appointment, completing vessel mapping, scheduling surgery, facilitating presurgical testing and then AV fistula maturation monitoring. When EMRs are used in this way, they move from passive data storage systems to valuable tools for care management and coordination [46].

Multidisciplinary care
Medical management of patients with late-stage CKD requires a care delivery model which supports the complexity of care for this patient group. The individual practitioner office paradigm may not be an optimal care delivery model in chronic disease [48]. There have been many calls for multidisciplinary predialysis clinics as an effective means to provide standard care to the CKD population [49]. Despite this, most countries still do not fund multidisciplinary care.

A starting point for developing an effective late-stage CKD multidisciplinary care model should be to examine existing model processes in countries such as Canada and England. In these systems, physicians utilize and implement a clinic model. CKD patients are referred and directed to see different disciplines at the same location including physicians, mid-level providers, dedicated CKD nurses, dieticians, pharmacists, social workers and vascular access nurses. The multidisciplinary care clinic has certain advantages [50]. It is ideal for promoting the use of protocols and reducing inappropriate care variability.

In the HT program, the most important aspect of multidisciplinary care is the role played by the nurse care managers. The nurses act as a bridge between physicians, improving the flow of information. By managing care processes between nephrologist visits, they mitigate the problem of episodic care. They improve communication by transmitting interappointment information about the patient to the nephrologist. The role of the nurse care manager is ‘supercharged’ by the informatics system that provides daily alerts that support evidence-based and effective care (see above).

Timely referral to nephrologist
It is generally accepted that appropriate timing of referral to a nephrologist to mitigate CKD complications is necessary. The specific glomerular filtration rate (GFR) level may vary based on patient complexity and other factors, but referral should never occur later than when the GFR is < 30 mL/min. Patients that present to the nephrologist ‘late’ often experience complications such as anemia, cardiovascular disease, mineral bone disease and malnourishment [51], which make initiation of RRT complex and prone to poor patient outcomes.

Insufficient preparation for RRT is another consequence of late referral to nephrologists. Data from a 2011 DOPPS study suggests that lack of predialysis nephrology care is associated with increased mortality. The USRDS reports that 80% of incident HD patients 2011 began dialysis with a catheter in place. Only 16.3% initiated HD with a mature AV fistula in place. In comparison, patients with more than 1 year under a nephrologist’s care were more likely to initiate HD with a mature AV fistula in place, at 31.9% [35].

Protocol use
In late-stage CKD, protocols and standardization of procedures could improve care and health outcomes. There is often resistance to the use of protocols as not being adequately responsive to individual patient needs (‘cookbook’ medicine) [52], but suboptimal outcomes of late-stage CKD patients indicate a need to reduce variability in care. However, even strongly evidence-based protocols and guidelines must have sufficient flexibility to enable physician judgment. In the HT program, protocols were
developed by a multidisciplinary team, often using existing practice guidelines. The HT protocols are activated by insertion into programmed database queries and reports. HT protocols for processes such as pre-emptive transplant preparation, home safety evaluation and risk stratification are managed collaboratively by the nurse and nephrologist. We have found that, just as checklists help even the most skilled pilots avoid errors, protocols help the HT care team achieve consistent, highly reliable care.

Patient engagement

In patients with chronic disease, active patient involvement in their health care can lead to better outcomes, and potentially lower costs [53]. Patient engagement refers to a patient’s knowledge, ability and willingness to manage his or her own health care, paired with interventions which promote positive patient behavior [53]. This process starts with patient and caregiver education about chronic kidney disease and requires reinforcement about natural history and complications. Education must be provided at a level appropriate for the patient’s learning ability. Patient engagement increases as he or she expresses preferences in the treatment plan, and finally treatment decisions are made based on patient preferences, medical evidence and clinician judgment. An important consideration is community engagement. A good example comes from Gubbio, Italy, where important improvements in blood pressure control were obtained in a small town [54]. A late-stage CKD program in Taiwan appears to be slowing progression to dialysis [55]. In the HT program, education is provided by nephrologists and nurses. It is preferred that key caregivers are present to learn along with the patient. HT education covers many subjects, but focuses on modality selection, diet and depression recognition. For diet, the approach is ‘Low Salt Every Day.’ In hypertension general compliance with a low salt diet is acceptable. In contrast in late CKD, with reduced salt and water excretion and frequent coexistence of CHF and LVH, even a single day of sodium excess may result in a hospitalization. Compliance must be very consistent.

Conclusion

The incidence of chronic disease is increasing and poses a major challenge to care providers and health systems around the world. CKD, while not yet a major global focus, affects a large number of patients and has great impact on mortality, quality of life and health-care costs. In particular, care of the late-stage CKD patients is complex, with many interacting medical comorbidities and multiple care providers. Evolution from current care models to more closely match the needs of late-stage CKD holds promise. By promoting communication between the patient and care providers, engaging patients in their health care, and leveraging innovative information technology, we propose a transformation from our current, reactionary health-care system into a proactive and collaborative care model.

Conflict of interest statement. None declared.

References

1. World Health Organization. 2008–2013 Action plan for the global strategy for the prevention and control of noncommunicable diseases: prevent and control cardiovascular diseases, cancers, chronic respiratory diseases and diabetes. 2008. http://www.who.int/nmh/publications/9789241597418/en/ (18 November 2014, date last accessed)
2. Ward BW, Schiller JS, Goodman RA. Multiple chronic conditions among US adults: a 2012 update. Prev Chronic Dis 2014; 11: E62
3. World Health Organization. Noncommunicable Diseases Country Profiles 2011 WHO Global Report. 2011. http://www.who.int/nmh/publications/ncd_profiles2011/en/ (18 November 2014, date last accessed)
4. Alwan A, Maclean DR, Riley LM et al. Monitoring and surveillance of chronic non-communicable diseases: progress and capacity in high-burden countries. Lancet 2010; 376: 1861–1868
5. Icks A, Haastert B, Trautner C et al. Incidence of lower-limb amputations in the diabetic compared to the non-diabetic population. Findings from nationwide insurance data, Germany, 2005–2007. Exp Clin Endocrinol Diabetes 2009; 117: 500–504
6. Resnikoff S, Pascolini D, Etya'ale D et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004; 82: 844–851
7. Mukherjee D, Patil CG. Epidemiology and the global burden of stroke. World Neurosurg 2011; 76: 585–590
8. Horton R. The neglected epidemic of chronic disease. Lancet 2005; 366: 1514
9. World Health Association. The World Health Report 2010—Health Systems Financing: the Path to Universal Coverage. 2010
10. American Heart Association. Heart Disease and Stroke Statistics—2014 Update. 2014. http://circ.ahajournals.org/content/early/2013/12/18/01.cir.0000441139.02102.80.full.pdf (29 July 2014, date last accessed)
11. National Cancer Institute. Cancer Prevalence and Cost of Care Projections. http://costprojections.cancer.gov/ (29 July 2014, date last accessed)
12. Robert Wood Johnson Foundation. Chronic Care: Making the Case for Ongoing Care. http://www.rwjf.org/content/dam/rwjf/reports/reports/2010/rwjf5458 (29 July 2014, date last accessed)
13. World Health Organization. Preventing Chronic Diseases: a Vital Investment. Geneva, 2005. http://www.who.int/chp/chronic_disease_report/en/ (18 November 2014, date last accessed)
14. World Economic Forum. Global Risks 2010: a Global Risk Network Report. Geneva, 2010. http://www3.weforum.org/docs/WEF_GlobalRisks_Report_2010.pdf (18 November 2014, date last accessed)
15. Amuna P, Zotor FB. Epidemiological and nutrition transition in developing countries: impact on human health and development. Proc Nutr Soc 2008; 67: 82–90
16. Abegunde DO, Mathers CD, Adam T et al. The burden and costs of chronic diseases in low-income and middle-income countries. Lancet 2007; 370: 1925–1938
17. Matsushita K, van der Velde M, Astor BC et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010; 375: 2073–2081
18. Keith DS, Nichols GA, Guillom CM et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004; 164: 659–663
19. Wen CP, Cheng TY, Tsai MK et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study

Late-stage kidney disease
