Kidney Disease in Elderly

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This is to acknowledge that Shani Shastri, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Shastri will not be discussing off-label uses in his/her presentation.

Biographical information

Dr. Shastri is originally from India and received her initial medical training at K.J. Somaiya Medical Center in Mumbai, India, followed by a Masters in Public Health degree at University of Loma Linda, California. She completed her Internal Medicine residency at the University of Massachusetts and Nephrology fellowship at Tufts Medical Center. During her fellowship, she also earned a master's degree in clinical research with a focus on epidemiology and outcomes. Clinically, she enjoys taking care of patients with a wide spectrum of kidney diseases, from acute illnesses to chronic kidney disease. Her research interests include investigations of aging and kidney disease, and cardiovascular disease and kidney disease.

Purpose and overview

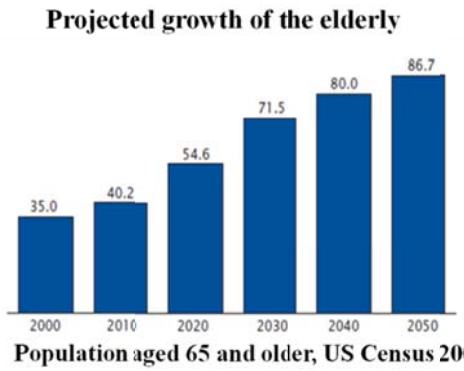
The goal of the presentation is review how biology of the aging process influences kidney function, to explain how aging influences the diagnosis of chronic kidney disease, the clinical significance of kidney disease in the elderly

Education objectives

1. Discuss effect of normal aging on kidney function
2. Assessment of kidney function in the elderly
3. Prevalence of chronic kidney disease in the elderly and its clinical significance
4. Review management of kidney disease in the elderly

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem primarily in the elderly. In various epidemiological studies, approximately one third to one half of the individuals older than 70 years have CKD.(1-3) Age was also the leading risk factor for incident CKD in the Framingham Heart Study.(4) Thus, older individuals are most likely both to have CKD and to develop CKD over time. According to the United States Census Bureau from 2005, 35 million persons were 65 years or older in 2000 and by 2030 this will increase to 72 million when the "baby boomers" reach old age.(5) In 2003, people aged 65 and older represented 12 percent of the total population and this is projected to increase nearly 20 percent of the total U.S. population by 2030. Those who are older than 80 years will have the fastest rate of growth with an expected increase to 19.5 million by 2030. In Europe, there is expected to be a similar growth rate in the elderly population from 6.9% of the population in 2000 to 12% of the population by 2030 (6). Given the projected growth of the elderly population, understanding the prevalence of CKD in the elderly has important clinical and economic consequences.

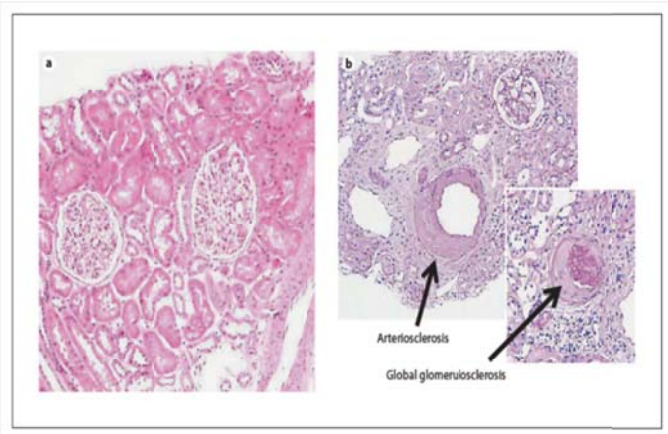


According to a recent report by the federal Agency for Healthcare Research and Quality 5% of patients account for nearly 50% of Medicare's $1.3 trillion expenditure. These patients are referred to as the "super-utilizers" or "high-frequency patients" or "frequent fliers", the costly cohort battling multiple chronic illnesses such as diabetes, kidney disease and heart failure.

AGING AND PHYSIOLOGICAL CHANGES OF THE KIDNEYS

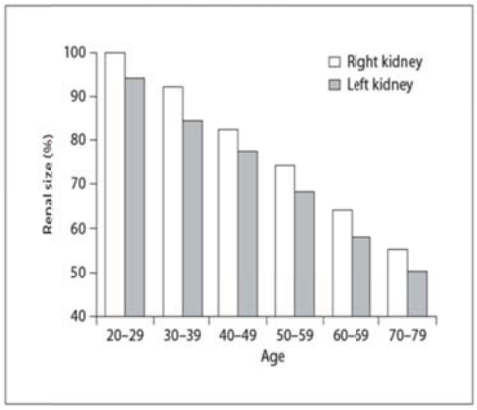
Aging is both a natural and inevitable biological process. With advancing age, the kidneys undergo anatomical and physiological changes that are not only the consequences of normal organ senescence but also of specific diseases (such as atherosclerosis or diabetes) that occur with greater frequency in older individuals. Distinguishing these two processes, one pathologic and the other physiologic can be challenging. How does the anatomy of the kidney change with 'natural and healthy' aging in the absence of either a specific kidney disease or CKD risk factors? Nephrosclerosis can be identified in kidneys by several different methods: gross appearance of a leathery granular kidney surface at autopsy, reduced kidney volume on an imaging study, or histologic findings from a cortical renal biopsy. Autopsy studies from apparently healthy aging individuals suggest that the "senile" kidney is characterized by nephron and kidney shrinkage, an increase in globally sclerotic glomeruli (also known as obsolescent glomeruli), a progressive loss of glomeruli (presumably via absorption of obsolescent glomeruli), preservation of the glomerular tubule volume relationships, and absence of glomerular hypertrophy. These findings appear to be a "universal" consequence of aging per se, although they might be influenced by concomitant co-morbidity.(7)

Histological abnormalities with aging



The average (median) histology for 20-year-old kidney donors show no chronic histological abnormalities (a) and for 70-year-old kidney donors shows 2 different chronic histological abnormalities (b) (in this example, global glomerulosclerosis and arteriosclerosis)

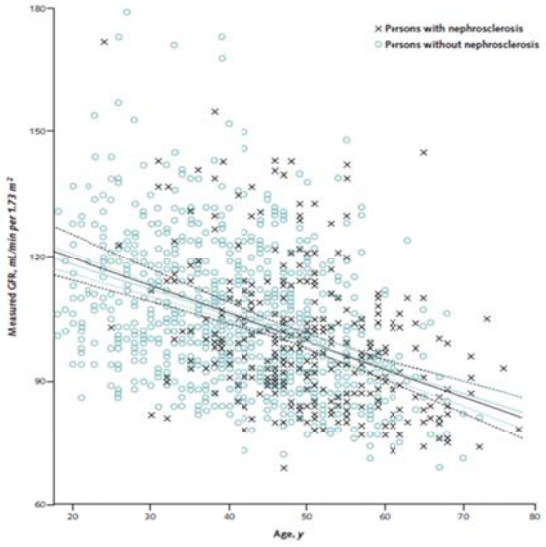
Renal size by age among 360 adults without kidney disease



Prassopoulos et al. AJR 1990

Living kidney donors provide a unique opportunity to gain insights into age-related changes in the renal parenchyma. It helps us evaluate the question whether senile nephrosclerosis account for the decline decline in glomerular filtration rate (GFR) with Aging? Rule et al. found that that the frequency of nephrosclerosis (defined by the presence of ≥2 of the parameters of global glomerulosclerosis, interstitial fibrosis, or arteriosclerosis) increased from about 3% in donors 18 to 29 years of age to 73% in donors 70 to 77 years of age.(8) Yet the decline in GFR with age did not differ between donors with or without nephrosclerosis on the kidney biopsy. Thus, the natural tendency for a decline in kidney function with aging does not appear to be explained simply by the appearance of nephrosclerosis per se.

Relationship between GFR and age in persons with and without nephrosclerosis

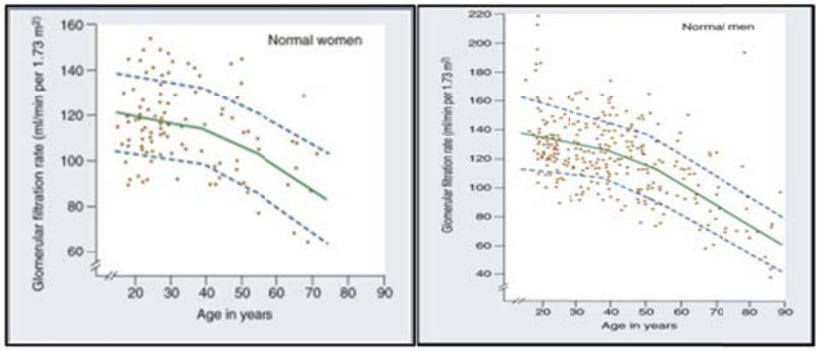


Rule AD et al. Ann Intern Med 2010

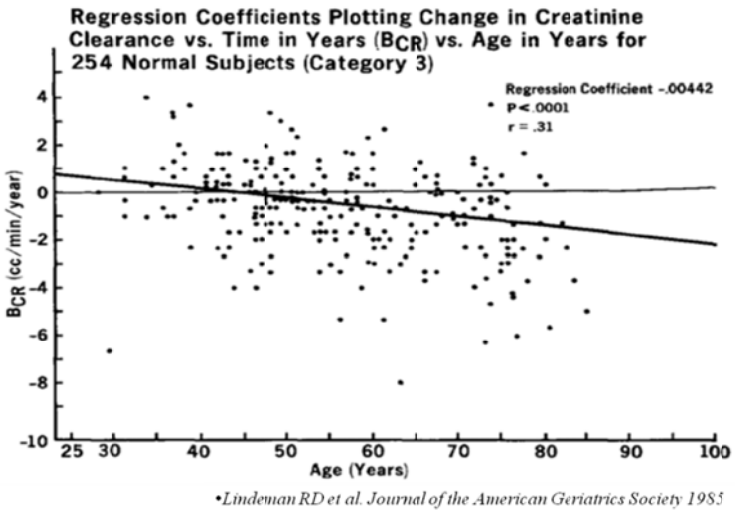
In a follow-up study they found that age differences in GFR, treated hypertension, nocturnal blood pressure, urine albumin excretion, family history of end-stage renal disease, body mass index, serum cholesterol, glucose, and uric acid also failed to account for this dramatic increase in nephrosclerosis with aging. Authors suggested the following reasons that may explain these findings: sampling error, decline in GFR with aging may represent a renal response to nonrenal pathology where less GFR may be needed to process metabolic waste because of age-related sarcopenia and lastly that the decline in GFR with aging could reflect reabsorption of glomeruli or other pathological changes in the kidney not detected by standard light-microscopic evaluation of a renal biopsy. It is important to note that donor evaluations do not include screening for subclinical vascular disease, and subclinical disease may have not been captured. Further studies are needed to understand age-related changes in renal morphology and function as this will have substantial implications on our understanding and management of CKD in the elderly.

CHANGES IN RENAL FUNCTION WITH AGE

Several cross-sectional studies of renal function indicate there is a progressive decline with age after the age of 40 years. Limited data are available to address the question of whether and how much renal function changes during healthy aging. In the Baltimore Longitudinal Study of Aging, true 24-hour creatinine clearance was measured among 884 community dwelling volunteers.(9) There was an accelerating decline in creatinine clearances with advancing age. Although mean creatinine clearance rates fell from 140 ml/min/1.73 m 2 at age 25-34 years to 97 ml/min/1.73 m 2 at age 75-84 years (a 31% difference), serum creatinine concentrations rose in significantly from 0.81 and 0.84 mg/100 ml. The proportionate decrease in creatinine production may be a reflection of the decrease in body muscle mass that occurs with age. Among 254 presumably 'normal' subjects (all men without renal disease or hypertension but some with non-proteinuric diabetes) healthy adults that were followed for ≥8 years with serial creatinine clearance measurements, the mean decrease in creatinine clearance was 0.75 ml/min/year.(10) The calculated slopes of creatinine clearance vs. time followed a normal Gaussian distribution. One third of all subjects followed had no absolute decrease in renal function (positive slope of creatinine clearance vs. time) and there was a small group of patients who showed a statistically significant increase (P less than 0.05) in creatinine clearance with age. The statistical analysis did not adequately account for imprecision of creatinine clearances measures, the limited number of observations, and multiple hypothesis testing; relatively few of the increasing slopes were likely a true increase in function. These limited data suggest that although on average there is an age-associated decline in renal function even among healthy adults, this does not seem to be an inevitable consequence of aging.



Wesson Jr LG: Renal Hemodynamics in Physiological States. 1969



•Lindeman RD et al. Journal of the American Geriatrics Society 1985

ASSESSMENT OF KIDNEY FUNCTION IN THE ELDERLY

Limitations of serum creatinine as an indirect measure of GFR are well recognized. Serum creatinine may remain normal or only mildly elevated in the setting of CKD and may lead to

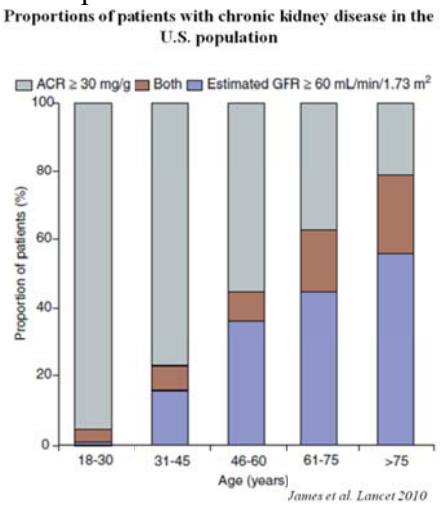
under recognition of CKD particularly among women and the elderly. In order to improve CKD recognition, predicting equations that consider serum creatinine in conjunction with age, sex, race, and body size as surrogates for the non-GFR determinants of serum creatinine are now being used as an alternative for GFR assessment. The most commonly used prediction equations include Cockcroft–Gault, the four-variable Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulae.(11) The MDRD equation is reasonably accurate at estimated GFRs of less than 60 mL/min per 1·73 m^2; however, bias and imprecision are increased at high estimated GFRs. The new (CKD-EPI) equation has less bias at high estimated GFRs and leads to a lower prevalence CKD in general population (11% vs 13% with MDRD Study equation), in women and white persons. However, the prevalence of CKD among the elderly remains similar with both equations in who bias was similarly low with both equations.(12)

Use of serum creatinine-based estimating equations may be particularly limited as a measure of estimated GFR in older adults in whom there may be a high prevalence of chronic disease associated with alterations in muscle mass and diet. Cystatin C is a cysteine protease inhibitor produced by nearly all human cells and excreted into the bloodstream. At a molecular weight of 13 kD, the protein is freely filtered by the renal glomerulus and then metabolized by the proximal tubule.(13) Cystatin C can have more advantages compared with creatinine because its non-GFR determinants are less affected by race and muscle wasting, and because it is more predictive of subsequent cardiovascular disease and mortality.(14) However, the non-GFR determinants of serum cystatin C are poorly understood. At the present time is unclear whether cystatin C should be used instead of serum creatinine to estimate renal function in older adults in the clinical setting. Confirmation of reduced estimated GFR by measurement of GFR (creatinine clearance or exogenous filtration markers) is warranted when decisions are dependent on accurate knowledge of GFR such as determination of eligibility for kidney donation or dose adjustment of toxic drugs that are excreted by the kidneys and occasionally if you need to confirm the presence of CKD.

Burden of CKD among Older Adults

In 2002, the National Kidney Foundation (NKF) published the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification provided standardized terminology for staging CKD and recommend identifying those with CKD based on routine laboratory measurements. These clinical practice guidelines aimed to improve outcomes by identifying CKD earlier in the course of the disease when treatment could potentially prevent the loss of kidney function and slow the progression of the disease. Because measuring GFR is not feasible in routine clinical practice, the guidelines recommended estimating GFR using prediction equations that take into account serum creatinine concentration. When this classification was applied to the general population, in National Health and Nutrition Examination Survey (NHANES) 1999, the overall prevalence of CKD was 13.1% with more than 40% of CKD in those over 70 years old. A graded increase in the prevalence of CKD noted older age groups.

The prevalence albuminuria increases progressively in the U.S. population after the age of 40 years. The increased prevalence is most marked in diabetic and hypertensive subjects but is also observed in patients lacking these risk factors. The prevalence of albuminuria is higher in African Americans, Mexican Americans, and those with reduced GFR. This is clinically relevant because albuminuria is an independent risk factor for cardiovascular disease and cardiovascular mortality.



Many cases of CKD in the elderly population manifest without a readily apparent cause; this is particularly true for CKD when defined only by reduced glomerular filtration rate. This has generated many questions and much controversy about whether a moderate reduction in estimated GFR without other evidence of kidney damage in the elderly population should be designated as a disease. Some believe it is inappropriate to diagnose CKD in elderly individuals on the basis of an estimated GFR of 45–60 ml/min per 1.73m2, because some of these people are unlikely to progressively lose kidney function. Labeling these individuals as having CKD is incorrect because their decrease in GFR may simply represent a normal, age-related decline in kidney function. Despite this controversy, there is consistent evidence that reduced estimated GFR and albuminuria, either separately or in combination, identifies a higher risk state in the elderly population as is evident from the many studies that demonstrate an association for both lower estimated GFR and albuminuria, with both a higher prevalence and an increased incidence of adverse outcomes. If reductions in estimated GFR do not reflect kidney disease, but rather a normal aging process, then reduced estimated GFR would not be associated with these complications. It is also proposed that from a historical perspective, the idea that hypertension was driving conditions such as stroke and cardiovascular disease was initially dismissed based on how common it was in the general population; the same situation could conceivably be the case of CKD.

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m²)	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

**Including nephrotic syndrome (albumin excretion usually 42200 mg/24 hours [ACR 42220 mg/g; 4220 mg/mmol]).

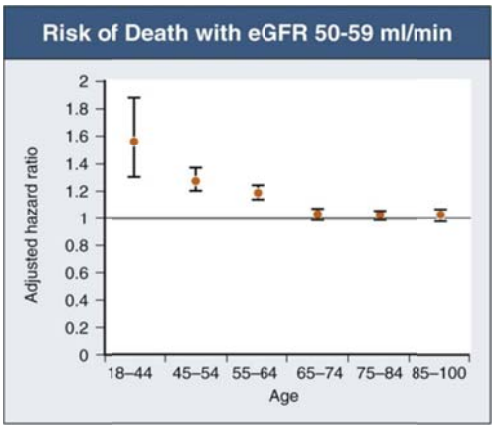
Kidney Disease Outcomes Quality Initiative (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of CKD

Since the original KDOQI 2002 classification was published, stage 3 CKD (a GFR of 30 to 59 mL/min per 1.73 m^2) has been subdivided into GFR stages 3a and 3b to more accurately reflect the continuous association between lower GFR and risk for mortality and adverse kidney outcomes. Also, albuminuria staging has been added because of the graded increase in risk for mortality, progression of CKD, and ESRD at higher levels of albuminuria, independent of eGFR. Predictive ability of albuminuria at all categories of GFR supports the suggestion to add albuminuria categories to all GFR categories. Since the relationship with albuminuria is continuous, the selection of the number of categories and the cutoff values appears arbitrary.

CLINICAL SIGNIFICANCE OF CKD IN THE ELDERLY

CKD and Mortality among Older Adults

It is well established that reduced GFR is associated with mortality, largely cardiovascular in the general population and the risk increases exponentially with decline in estimated GFR. Several studies have noted an attenuation of the prognostic importance of kidney function with advancing age. Few studies that compared mortality risk associated with CKD across all ages, found that the relative risk for death associated with each level of kidney function decreased markedly with age, and creatinine-based estimated GFR of 50 to 59 ml/min/1.73m^2 and 45–59 ml/min/1.73m^2 was not associated with an increased risk of death compared to the referent group (eGFR $\geq$ 60 ml/min/1.73m^2) among those older than 65 and 75 years of age, respectively.(1; 15)



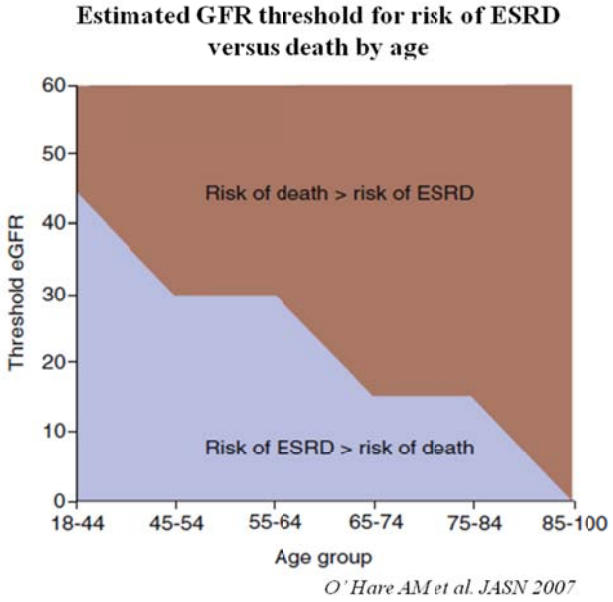
O' Hare AM et al. JASN 2006

Among octogenarians in Cardiovascular Health Study (CHS) All Stars participants, the association between estimated GFR_{CR} and all-cause mortality differed from that observed with $eGFR_{CYS}$, where the relationship was U-shaped for $eGFR_{CR}$, while for cystatin C the risk was primarily present in the lowest quintile.(16) In contrast, in a meta-analysis of general population cohorts conducted by the Chronic Kidney Disease Prognosis Consortium (CKD-PC), investigators evaluated the association between eGFR less than 60ml/min/1.73 m2 and increased risk for all-cause and cardiovascular mortality among adults less than 65 years of age and their counterparts greater than or equal to 65 years of age(17). Reduced estimated GFR was associated with increased hazards for all-cause mortality among individuals less than 65 years of age and greater than or equal to 65 years of age. These studies stratified at an age of 65 years and did not provide information in older age groups. Higher levels of albuminuria have been reported to be associated with increased mortality in prior studies of older adults with diabetes mellitus and in the general population.

Risk of ESRD among the elderly

The incidence of end stage renal disease (ESRD) increases exponentially as estimated GFR decreases. Mortality rates also increase with falling estimated GFR, but this increase is more linear and far less dramatic. Among elderly it is important to recognize that risk for death tends to exceed that of ESRD at most levels of estimated GFR, whereas in younger patients, risk for

ESRD may exceed that of death at relatively higher levels of estimated GFR. (18) Understanding



each patient's relative risk for each of these competing outcomes needs to be taken into consideration when it comes to planning for future care needs.

Concurrent CKD Complications among Older Adults

Age-specific (<60, 60–69, 70–79, and ≥ 80 years) associations between estimated GFR and six concurrent CKD complications (anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism and hypertension) among NHANES and VA participants were examined. In both studies, higher prevalence of the metabolic complications was found at lower estimated GFR levels for all age groups.(19) These studies suggest that reduced kidney function in older patients is not benign and puts people at increased risk for the metabolic complications typically associated with CKD; however, both studies were limited by a cross-sectional design and temporal associations could not be assessed.

Hypertension in the elderly

Among NHANES III (1988–1994) subjects aged ≥60 years of age, either treated or not treated for a high BP, there was a J-shaped relationship between BP and CKD prevalence. Thus, persons with a BP of 120 – 159/80-99 mmHg had the lowest CKD prevalence, with a higher prevalence associated with a systolic BP <120/80 mmHg and a systolic BP ≥160/100 mmHg. Analyses of data from the Kidney Early Evaluation Program (KEEP), as well as NHANES, indicate that with increasing age, there is an increase in the prevalence and severity of CKD, confirming the strong relationship between BP and CKD in the elderly. With respect to the characteristics in hypertensive older patients when compared with younger patients (18 to 39 years of age in 2007 to 2008), older patients were more likely to be aware of their hypertension (84 versus 66 percent), more likely to be treated (80 versus 50 percent) and once treated, less likely to achieve blood pressure control (64 versus 82 percent). It is well known that hypertension in the aged is a major risk factor for all major aspects of cardiovascular disease, including coronary ischemic

events, heart failure, peripheral vascular disease, and stroke. Several studies have shown that with aging, systolic pressure in adults remains relatively constant up to approximately age 40 years, then rises progressively, whereas diastolic pressure rises progressively to age 50 years, then decreases so that pulse pressure (systolic minus diastolic), which is constant to age 40 years, begins to markedly rise after age 50 years. Furthermore the coronary risk was best predicted by diastolic pressure up to only age 40 years, by systolic pressure between 40-60 years, and by pulse pressure after 60 years.

A 2009 Cochrane review that included 15 studies RCTs and approximately 24,000 subjects >60 years of age in which subjects with a BP >140mm/90 mmHg at baseline received either placebo or a BP-lowering agent found that treatment reduced total mortality (RR 0.90; 95% CI 0.84–0.97) and total cardiovascular mortality and morbidity (RR 0.72; 95% CI 0.68–0.77), particularly due to a reduction in the incidence of stroke.(20) In very elderly patients ≥ 80 years the reduction in total cardiovascular mortality and morbidity was similar; however, there was no reduction in total mortality.

There is little evidence specific to the elderly with known CKD, although some inferences might be drawn from BP studies in elderly populations not specifically chosen for the presence of CKD. An effect of antihypertensive treatment on cardiovascular outcomes in the elderly in four major clinical studies is shown in the table. One important caveat is that HYVET-eligible patients were generally healthier than the general very old population and prevalence of baseline cardiovascular disease was low at only 12%. Two studies that were that had treat-to-target design trials failed to show any benefit in treating elderly patients to an SBP target of lower than 140 mm Hg compared with SBP targets lower than 150 and 160 mm Hg (JATOS and VALISH). In both studies, fewer efficacy outcome events occurred than were predicted and only about 15% of subjects had existing cardiovascular disease.

Effects of antihypertensive treatment on cardiovascular outcomes in the elderly

Parameter	HYVET	SHEP	STOP	Syst-Eur
Mean treatment BP reduction, SBP/DBP, mmHg	−29/−13	−27/−9	−29/−17	−23/−7
Stroke, % reduction	−30	−32	−47	−42
Coronary disease, % reduction	−23*	−27	−13	−30
Heart failure, % reduction	−64	−55	−51	−29

SHEP: Systolic Hypertension in the Elderly Program; STOP: Swedish Trial in Old Patients; HYVET: Hypertension in Very Elderly Trial; Sys-Eur: European Systolic Hypertension in the Elderly; Syst-China: Chinese Trial on Isolated Systolic Hypertension in Elderly. * Percentage of cardiovascular mortality reduction.

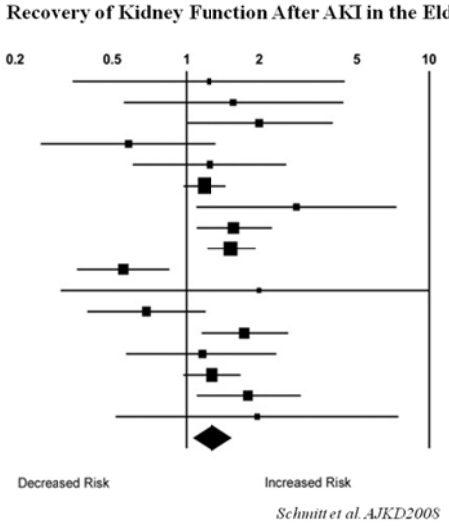
Burney B et al. Semin Nephrol 2009

While this confirms there is benefit in treating hypertension in the elderly, there is uncertainty about the optimal BP that should be achieved. The recent KDIGO 2012 guidelines recommends "Tailor BP treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects"(Not Graded). It is important to note that the pharmacology and pharmacodynamics of BP drugs change with age, mainly because of reduced GFR, but also due to changes in hepatic function, and volume of distribution. All antihypertensive drugs may predispose the elderly patient to symptomatic orthostatic and postprandial hypotension, syncope, and falls. SPRINT- an ongoing clinical trial randomizing patients without diabetes or significant proteinuria to a systolic BP of <140mmHg or < 120mmHg is likely to provide important evidence to guide BP management as it contains both elderly patients and those with CKD.

Acute kidney injury in the elderly

Several epidemiological studies have noted that elderly subjects are at increased risk of AKI and there is age-dependent relationship between AKI and older age. In study by Joannidis *et al.* analyzed 16,784 patients during the initial 48 hours of their intensive care unit stay. The incidence of AKI was found to range between 28.5 and 35.5% when applying AKIN and RIFLE criteria, respectively.(21) The mean age was 63 years, and 25% of patients were older than 75 years. Hsu et al. noted that the incidence of non-dialysis and dialysis-requiring AKI among members of a large integrated health care delivery system –Kaiser Permanente of Northern California that the incidence of AKI had increased from 1996 to 2003, and this increase was most dramatic in patients aged ≥80 years.(22) Factors predisposing the elderly to AKI include i) age related structural and functional alterations resulting in reduction in functional renal reserve, decreased glomerular filtration rate, impaired renal auto regulation, defective fluid homeostasis ii) comorbid conditions that may facilitate AKI such as renovascular disease and congestive heart failure; and iii) increased susceptibility to drug toxicity. Thus older adults are vulnerable to acute stress and more likely to develop clinically relevant AKI.

Acute kidney injury is associated with significant morbidity, mortality and health care costs. The short-term mortality for elderly patients with AKI ranges from 15%-40% depending on the setting, definition of AKI, and specific age cutoffs. Two studies have noted that in-hospital mortality associated with AKI have declined over time even in the elderly despite an increase in degree of co-morbidity.(23) Long term risk of mortality is increased after AKI though the impact of AKI is diluted with aging as a result of the cumulative effects of other competing co-morbidities. The risk of CKD and ESRD is increased after AKI in the elderly, however; whether this relationship is truly causal, or related to residual confounding remains unclear.(23)



The mainstay of AKI management is early diagnosis and prevention. The treatment of AKI in the elderly is no different from other age groups as literature does not support inferior outcomes in elderly patients requiring dialysis. However, decisions to pursuit aggressive support modalities such as renal replacement therapy should include a careful assessment of comorbid conditions, prognosis for meaningful recovery, and quality-of-life issues. Given the limited therapeutic options for AKI and the significant impact of AKI on outcomes, it is imperative that preventive strategies be used whenever possible.

General approaches to the prevention of AKI in the elderly

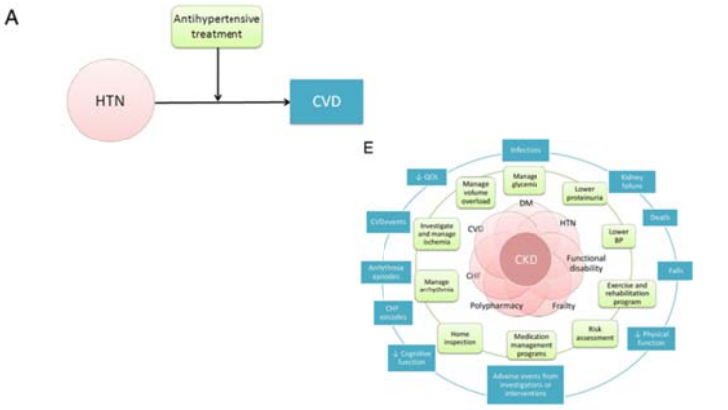
Early recognition	Early recognition of at-risk patients (i.e. CKD)
	Recognition of high-risk clinical settings
	Determine small changes in creatinine or drop in UO
	Recognition of potential nephrotoxins
Avoidance of nephrotoxin exposure	Avoid concomitant use of multiple nephrotoxins
	Use of lowest dose and for shortest time period
	Monitor drug levels if applicable
	Frequent monitoring of renal function
	Drug-specific measures (liposomal amphotericin, once daily for aminoglycosides)
Prophylaxis for contrast exposure	Avoid contrast medium, or at least delay contrast use if patient at risk
	Always use lowest possible quantity of contrast
	Use hypo or iso-osmolar and non-ionic contrast
	Adequate volume repletion
Avoid agents that impair renal blood flow autoregulation	i.e. NSAIDs
Determine correct medication dose for eGFR	
Perioperative optimization	Differ surgery in at-risk patients if possible
	Initiate appropriate monitoring (hemodynamic, intra-abdominal pressure)
	Early and guided optimization of volume status and hemodynamics
	Limit exposure to nephrotoxins
Infection and sepsis	Low index of suspicion for early diagnosis
	Diagnose/treat sepsis-related intravascular volume depletion
	Early and appropriate antibiotic initiation
	Early guided volume repletion, avoid high molecular weight hydroxyethylstarch

MANAGEMENT OF CKD

Evidence for interventions recommended in clinical practice guidelines are often based on the results of clinical trials that did not enroll a representative sample of older adults. Thus the benefits and harms of many recommended interventions are unknown in older adults. It can be difficult to extrapolate available evidence from younger trial populations to real-world populations of older adults if there are systematic differences between these populations. The management of CKD does not vary based on age and includes treatment of disorders of fluid and electrolyte balance, such as volume overload, hyperkalemia, metabolic acidosis, and hyperphosphatemia, as well as abnormalities related to hormonal or systemic dysfunction, such as anorexia, nausea, vomiting, fatigue, hypertension, anemia, malnutrition, hyperlipidemia, and bone disease.

Drug levels in older adults with CKD can be affected by decreased filtration, impaired tubular function, or by altered renal metabolism. In many CKD patients, serum albumin is lower than normal and protein binding and bioavailability of metabolites must be considered. This may pose greater risks to those with impaired kidney function because of impaired clearance or drug–drug reactions. Clinical trials provide guidance for the initial approval and indications for medications, but often exclude older adults or those with impaired kidney function, so reliable data regarding safety profiles of commonly used medications in this population are limited.

Clinical practice guidelines present standardized and evidence-based approach care with the goal to provide a simplified model to guide management on single disease. Most guidelines do not stratify their recommendations for older versus younger adults, do not consider burden of comorbid illnesses, or do not specifically state the expected time frame for a favorable risk-benefit ratio. Older individuals generally have more than one disease process. There is often rift between what might be recommended in clinical practice guidelines and what might be most beneficial for an individual patient. Clinicians can find it challenging to manage individuals with CKD by using disease-oriented models of care because of prevalence of complex comorbid conditions in this patient population, competing health priorities and conflicting treatment recommendations. Boyd et al provided a hypothetical case to illustrate how disease-based guidelines may be harmful in older adults with complex comorbidity(24). Circles indicate diseases, rectangles outcomes, and rounded rectangles treatments. Disease models show treatment of (A) hypertension (HTN) without CKD; (E) CKD in older patients, incorporating clusters of common comorbid conditions as well as geriatric syndromes.



Uhlig K, Boyd C: Am J Kidney Dis 2011

In an older patient with a fairly standard set of comorbidities, these authors modeled the onerous pharmacologic and nonpharmacologic treatment regimen with multiple potential drug interactions and competing treatment priorities that would result if all relevant practice guidelines were followed.

Recently there has been a focus on individualized patient-centered models of care which emphasizes on modifiable outcomes that matter to patients. This may be more appropriate in older adults with CKD in whom there is a complex interplay between pathologic processes, aging, social, psychological, and other factors. By this approach, patient preferences are prioritized for example survival may be of less importance to older adults than other outcomes, such as quality of life, functional status, pain control, and independence. With patient-centered approach the disease-specific diagnoses and management are incorporated into individualized treatment plans and how they get incorporated depends on the extent to which disease-based recommendations are aligned with preferences and goals of patients. Thus this approach can result in diverse treatment plans for older adults with similar stages of CKD. Nephrologists will need to become skilled in the art and science of eliciting patient goals and preferences and then incorporate these into treatment strategies. Heterogeneity in treatment goals may make it

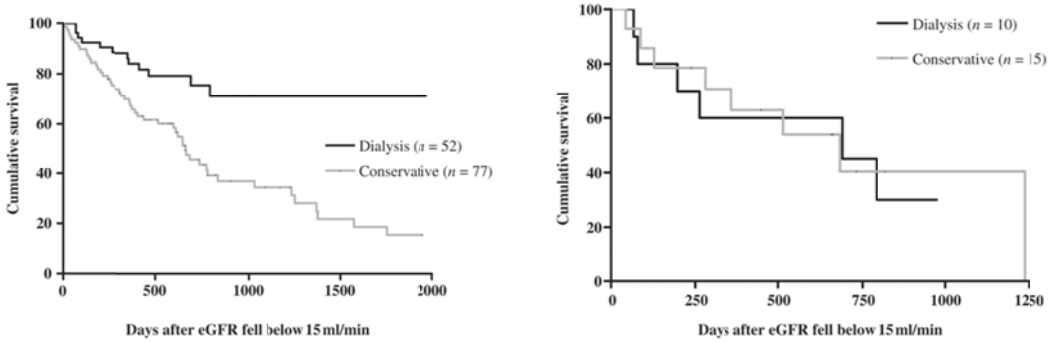
difficult to evaluate the effectiveness of care but more studies are needed to evaluate the role of patient-centered care in treatment decisions and to determine how these approaches impact outcomes that matter most to patients.

Renal replacement therapy in the elderly

Both the incidence and prevalence of ESRD are higher in older subjects. The rate of patients >75 years of age initiating dialysis has grown substantially in the U.S. over the past two decades. This has to do with several factors, including improvements in medical technology enabling people to live long enough to develop advanced CKD, but also an increasing expectation for aggressive medical care late in life. Median survival after dialysis initiation for adults ages 75 to 79, 80 to 84, 85 to 89, and ≥90 years is 1.7 years, 1.3 years, 0.9 years, and 0.6 years, respectively; however, considerable heterogeneity in survival exists among patients of similar ages, highlighting the limitations of using age alone to predict outcomes. In-center dialysis is the most commonly used treatment for older patients with ESRD. Patients over 65 tend not to choose peritoneal dialysis for a host of reasons, not the least of which is peritoneal dialysis is underutilized in the US in general. Peritoneal dialysis is a continuous home-based therapy, which offers several potential advantages in older people, less disruptive for a patient's and their family's lifestyle, avoids the need for transport and furthermore, the rapid changes in hemodynamic and fluid status associated with hemodialysis are often poorly tolerated by older patients who often comment on feeling 'washed out' after a dialysis session. However, a recent study suggests that PD may be preferable to HD in the elderly, at least for those with the cognitive and functional ability to perform PD. The BOLDE (Broadening Outcomes for Long-term Dialysis in the Elderly) trial out of the UK looked at health-related quality of life measures in PD vs HD patients over 65. Overall, in two closely matched demographic groups of older dialysis patients, QOL was similar, if not better, in those on PD.

The risks attendant to dialysis may be amplified in the older patient and patients with impaired functional status or comorbid conditions, and therefore, dialysis may confer little to no survival benefit. The degree of co-morbidity a patient has is a much better predictor of how they will do on dialysis than age alone. In study by Murtagh et al, the investigators performed a retrospective analysis of 129 patients > 75 years of age who were referred to a multi-disciplinary pre-dialysis care clinic. They compared patients who chose dialysis with those who chose "conservative care"--which involved the decision to NOT begin dialysis but rather attempting to control their symptoms with blood pressure control, diet, etc.

Comparing the dialysis vs. conservative management in the elderly



Murtagh F E M et al. Nephrol. Dial. Transplant. 2007

One- and two-year survival rates were 84% and 76% in the dialysis group and 68% and 47% in the conservative group, respectively, with significantly different cumulative survival. However, this survival advantage was lost in those patients with high comorbidity scores, especially when the comorbidity included ischaemic heart disease.(25) Patients >75 years of age with Stage V CKD and underlying ischemic heart disease should know that their likelihood of dying with or without dialysis is virtually the same.

Rates of dialysis withdrawal are highest among the oldest patients, raising the possibility that the standard content of informed consent for dialysis warrants an age-sensitive approach and should include presentation of risks, benefits, and burdens associated with dialysis, age-specific estimates of prognosis with and without dialysis, and potential for loss of independence and decline in functional status with initiation of dialysis. A systematic approach to advance care planning for patients nearing ESRD and the integration of shared decision making into medical care is espoused in the Renal Physicians Association guideline.(26)
Transplantation should be considered in the management of elderly patients with ESRD because studies have clearly shown that the elderly recipient benefits from renal transplantation by a significant reduction in mortality (41%) compared with wait-listed ESRD patients. One study showed that kidney transplantation was cost effective for patients greater than age 65, but that the attractiveness of transplantation declined as waiting time increased. The expanded criteria donor (ECD) list shortens waiting times at the cost of a higher risk of allograft loss. For older patients, the benefit of an ECD kidney appears to outweigh the risks and thus is a common among older transplant recipients.

SUMMARY

The fastest growing group of people in the United States who have impaired kidney function is the oldest age group. The presence of CKD identifies a higher risk state in the elderly population, with increased risk for multiple adverse outcomes, including death, cardiovascular disease, cognitive impairment, and kidney failure. Age and stage of kidney disease seem to modify prognosis with elderly more likely to die than progress to ESRD as compared with a younger cohort. Moreover, the incidence of death at all stages of kidney disease was higher in the elderly as compared with the younger cohort. Future studies that explore novel therapeutic approaches to reduce CVD and mortality among those with reduced kidney function are needed in the elderly.

References:

1. O'Hare AM, Bertenthal D, Covinsky KE, Landefeld CS, Sen S, et al. 2006. Mortality risk stratification in chronic kidney disease: one size for all ages? *J Am Soc Nephrol* 17:846-53
2. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, et al. 2007. Prevalence of chronic kidney disease in the United States. *Jama* 298:2038-47
3. Garg AX, Papaioannou A, Ferko N, Campbell G, Clarke JA, Ray JG. 2004. Estimating the prevalence of renal insufficiency in seniors requiring long-term care. *Kidney Int* 65:649-53
4. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. 2004. Predictors of new-onset kidney disease in a community-based population. *Jama* 291:844-50
5. 2005. United States Census Bureau
6. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, et al. 2006. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 17:2275-84
7. Choudhury D ML. 2007. *Aging and kidney disease*. WB Saunders. 681-93 pp.
8. Rule AD, Cornell LD, Poggio ED. 2011. Senile nephrosclerosis--does it explain the decline in glomerular filtration rate with aging? *Nephron. Physiology* 119 Suppl 1:p6-11
9. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. 1976. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *Journal of gerontology* 31:155-63
10. Lindeman RD, Tobin J, Shock NW. 1985. Longitudinal studies on the rate of decline in renal function with age. *Journal of the American Geriatrics Society* 33:278-85
11. Levey AS, Stevens LA. 2010. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis* 55:622-7
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, et al. 2009. A new equation to estimate glomerular filtration rate. *Annals of internal medicine* 150:604-12
13. Fliser D, Ritz E. 2001. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am J Kidney Dis* 37:79-83
14. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, et al. 2005. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 352:2049-60
15. Raymond NT, Zehnder D, Smith SC, Stinson JA, Lehnert H, Higgins RM. 2007. Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. *Nephrol Dial Transplant* 22:3214-20
16. Shastri S, Katz R, Rifkin DE, Fried LF, Odden MC, et al. 2012. Kidney function and mortality in octogenarians: Cardiovascular Health Study All Stars. *Journal of the American Geriatrics Society* 60:1201-7
17. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. 2010. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 375:2073-81
18. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, et al. 2007. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol* 18:2758-65

19. Bowling CB, Inker LA, Gutierrez OM, Allman RM, Warnock DG, et al. 2011. Age-specific associations of reduced estimated glomerular filtration rate with concurrent chronic kidney disease complications. *Clin J Am Soc Nephrol* 6:2822-8
20. Musini VM, Tejani AM, Bassett K, Wright JM. 2009. Pharmacotherapy for hypertension in the elderly. *The Cochrane database of systematic reviews*:CD000028
21. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, et al. 2009. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive care medicine* 35:1692-702
22. Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM, Go AS. 2007. Community-based incidence of acute renal failure. *Kidney Int* 72:208-12
23. Coca SG. 2010. Acute kidney injury in elderly persons. *Am J Kidney Dis* 56:122-31
24. Uhlig K, Boyd C. 2011. Guidelines for the older adult with CKD. *Am J Kidney Dis* 58:162-5
25. Murtagh FE, Marsh JE, Donohoe P, Ekbal NJ, Sheerin NS, Harris FE. 2007. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrol Dial Transplant* 22:1955-62
26. Association RP. 2010. *Clinical Practice Guideline for Shared Decision Making in the Appropriate Initiation and Withdrawal from Dialysis*.