Chapter 4: Other complications of CKD: CVD, medication dosage, patient safety, infections, hospitalizations, and caveats for investigating complications of CKD

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This section addresses a series of important topics which impact the outcomes of people with CKD. Specifically CVD, interpretation of tests for CVD, infections, vaccinations and hospitalizations, medications, and patient safety are addressed. This section is designed to help the practitioner appreciate the specific nuances related to testing and drug administration in people with CKD and to alert all clinicians to the fact that many common tests may not be as useful in people with CKD to diagnose or evaluate therapies. It was beyond the scope of the guideline and evidence review to thoroughly evaluate all tests with respect to sensitivity and specificity in different groups of people with CKD but future research may consider this as a useful direction.

4.1 CKD and CVD

Population-based studies have demonstrated an increased risk of death and cardiovascular mortality as GFR falls below 60 ml/min/1.73 m^2 or when albumin is detected on urinalysis. This is not explained by an increase in traditional risk factors. There are CKD-specific risk factors associated with more advanced CKD which drive the high rates of mortality and morbidity even at young ages. People with CKD are more likely to experience a cardiovascular event than to progress to ESRD, have a worse prognosis with higher mortality after acute myocardial infarction (MI), and have a higher risk of recurrent MI, heart failure and sudden cardiac death. Management of modifiable cardiovascular risk factors, such as improved BP and diabetes control, also reduces CKD progression.

4.1.1: We recommend that all people with CKD be considered at increased risk for cardiovascular disease. (*1A*)

RATIONALE

This statement is worded in this way to reflect the strong and independent associations between GFR and albuminuria categories and risk of CVD in people with CKD and applies to both adult and pediatric populations.

Evidence Base

Large cohort studies have demonstrated the strong and independent associations between CVD (acute coronary syndrome [ACS], stroke, heart failure and sudden cardiac death) and CKD by category of eGFR, after adjusting for known CVD risk factors, history of CVD events, and proteinuria. In those with an eGFR of 45-59 ml/min/1.73 m^2, risk is increased by 43% and in those with eGFR below 15 ml/min/1.73 m^2, risk is increased by 343%.[58] Although people with GFR category G5 (GFR $<$ 15 ml/min/1.73 m^2) are at the highest risk of a CVD event, there will be more events in people with GFR categories G3a-G3b (GFR 30–59 ml/min/1.73 m^2) because of the much higher prevalence at these categories.[420] These events occur at a younger age in people with CKD suggesting that CKD promotes CVD at an accelerated rate.[421] The prognosis after an acute event is related to level of GFR with a significant rise in mortality when eGFR falls below 45 ml/min/1.73 m^2.[422–424]

Albuminuria is associated with duration and severity of hypertension; an adverse lipid profile with higher levels of total cholesterol, triglycerides and lipoprotein(a) and low HDL-C levels;[425] and abnormalities of coagulation. The presence of higher levels of proteinuria increases the risk of mortality and MI independently of level of eGFR.[426] Many studies have demonstrated low levels of urinary albumin to be associated with the increased risk of CVD in people with diabetes independent of renal function; however population studies of non-diabetic individuals have confirmed that even small amounts of albuminuria are associated with increased CVD risk. In the Third Copenhagen study, in people with microalbuminuria, risk of coronary heart disease was increased independently of age, sex, renal function, diabetes, hypertension, and plasma lipids.[427] The Chronic Kidney Disease Prognosis Consortium demonstrated that in general practice cohorts there was an increase in cardiovascular mortality when ACR is higher than 30 mg/g (3 mg/mmol).[4] Analysis of data from the Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that any degree of albuminuria is a risk factor for cardiovascular events in individuals with or without diabetes.[428] The lack of a threshold of albuminuria for cardiac risk was also confirmed in the HUNT 2 Study[429] and the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study in patients with LVH.[430] Albuminuria and low eGFR were synergistic cardiovascular mortality risk factors in the HUNT 2 study and using both ACR and eGFR improved

cardiovascular risk stratification at all age levels, but particularly in persons 70 years and over.[429]

In the MDRD Study cohort of patients with GFR categories G3a-G4 (GFR 15–59 ml/min/1.73 m^2), cystatin C level was strongly associated with all-cause and cardiovascular mortality particularly in the elderly.[431] Analysis of data from MESA and the Cardiovascular Health Study (CHS) demonstrated that the worst prognosis of CVD, heart failure, and progressive CKD was found in those subjects with CKD diagnosed using the cystatin C-based equation.[432]

LVH is common with CKD, is known to reflect target organ damage, and is associated with increased cardiovascular mortality in CKD.[360] It is also important to consider the role of CKD-specific risk factors particularly in patients with more severe CKD (GFR <30 ml/min/1.73 m^2) and correct them where possible. Anemia has been thought to have a particular role in the early development of CVD in people with CKD. Although treatment of anemia is associated with improved well-being and greater exercise capacity, the results of several RCTs of anemia correction have suggested that complete correction of anemia is not advisable in people with lower GFR (<60 ml/min/1.73 m^2). A meta-analysis of 9 RCTs comparing different target Hb levels suggests an increase in mortality and worse BP control with the higher treatment targets, independent of the GFR category.[433,434] Those patients with LVH at baseline, a sign of target organ damage and which was present in 47% of the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta Trial (CREATE) cohort, had significantly worse cardiovascular outcomes when treated to the higher targets.[435]

Abnormalities of mineral metabolism with low 1,25-dihydroxyvitamin D and PTH were found to occur early in CKD in the Study for the Evaluation of Early Kidney disease [SEEK] study, however serum calcium and phosphate were usually normal until eGFR fell below 40 ml/min/1.73 m^2.[367] An association between elevated serum phosphate and cardiovascular mortality was demonstrated in a prospective study of people with CKD and this was also thought to be associated with low vitamin D levels.[436]

Pediatric Considerations

While the majority of data for, and evidence of, the high risk of cardiovascular morbidity and mortality in the pediatric renal population stems from the ESRD (dialysis and transplant) populations,[437–440] there is recognition that many if not all of the factors responsible for such outcomes will develop much earlier in this course of CKD. In fact, the current American Heart Association's guidelines for reduction of cardiovascular risk in pediatrics stratified the child with CKD to the highest risk category.[441]

Based on data from the CKiD trial, Wilson et al.[442] demonstrated extremely high prevalence rates for four traditional cardiovascular risk factors (hypertension, dyslipidemia, abnormal glucose metabolism, and obesity) in a subgroup of this cohort of 586 children with iohexol GFR proven mild to moderate CKD. In this cross-sectional analysis of 250 children who had data on all variables of interest, median GFR of 45.2 ml/min/1.73 m^2 (IQR 34.6-58.2), the prevalence of hypertension was 46%, dyslipidemia was 44%, abnormal glucose metabolism was present in 21%, and obesity in 15%. Hypertriglyceridemia was common, seen in 33%. In aggregate, only 26% of the cohort had no risk factors present, 39% had at least one and 22% had two, 11% had three and 2% had all four risk factors present. The prevalence of all these factors remained elevated even when the population was restricted to those defined as lean, BMI $<85^{th}$. In this group, the presence of 2 or 3 cardiovascular risk factors was still seen in 20% and 2%, respectively. Within the lean group 12% demonstrated abnormal glucose metabolism. Finally, multivariate regression analysis of their data demonstrated that glomerular disease as a cause of CKD and the presence of nephrotic range proteinuria were associated with much higher odds of having cardiovascular risk factors, 1.96 (95% CI 1.04-3.72) and 2.04 (95% CI 0.94-4.43), respectively.

It is also well-recognized that carotid intimal media thickness and pulse wave velocity changes, as potential surrogate measures for vascular damage in children, can be increased in in children with CKD.[443,444]

For further detailed discussions of the pathophysiology and complexity of CVD in the pediatric CKD population, two recent review papers from Mitsnefes[445] and Shroff et al.[446] are suggested. Both papers identify and discuss the pathophysiology of both traditional and CKD-specific cardiovascular risk factors as seen in this population.

4.1.2: We recommend that the level of care for ischemic heart disease offered to people with CKD should not be prejudiced by their CKD. (*1A*)

4.1.3: We suggest that adults with CKD at risk for atherosclerotic events be offered treatment with antiplatelet agents unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefits. (*2B*)

RATIONALE

These statements are worded in this way to reflect the growing body of evidence that suggests that treatment of traditional risk factors in CKD patients is of benefit, and that attempts to modify or preclude usual investigations and therapies are not necessary in CKD patients. Inasmuch as CKD populations have been understudied, but likely inadvertently included in larger population studies, the rationale for risk factor modification is similar to that in the general population. Modification of risk factors includes:

1. Smoking cessation
2. Exercise
3. Weight reduction to optimal targets
4. Lipid modification recognizing that the risk reduction associated with statin therapy in adults with CKD is

relatively constant across a broad range of baseline low-density lipoprotein cholesterol (LDL-C) levels
5. Optimal diabetes control HbA_{1C} <7% (53 mmol/mol)
6. Optimal BP control to <140/90 mm Hg or <130/80 mm Hg in those with CKD and depending on the degree of proteinuria (see Recommendations 3.1.4 and 3.1.5)
7. Aspirin is indicated for secondary prevention but not primary prevention
8. Correction of anemia to individualized targets (see *KDIGO Clinical Practice Guideline for Anemia in CKD*[11])

Evidence Base

The maintenance of cardiovascular health ultimately impacts 'kidney health' given the links between cardiac function, renal perfusion, atherosclerosis, and glomerulosclerois. The details of this complex biology are beyond the scope of these guidelines, but can be found in key references below.

There is evidence in the general population that smoking cessation is associated with a reduction in cardiovascular risk. In CKD there is evidence that smoking is associated with progression of renal disease, though no specific data exist that support cessation of smoking and delay of progression.[447]

People with CKD have reduced levels of muscle strength and aerobic activity. In those not on dialysis, exercise training is shown to improve functional capacity and BP.[448]

Weight loss in obese CKD patients can reduce rate of decline, proteinuria, and BP.[354]

The Study of Heart and Renal Protection (SHARP)[449] is the largest RCT in people with CKD to date. The results demonstrate that a lipid-lowering strategy which included fixed dose simvastatin and ezetimibe resulted in a 17% reduction in atherosclerotic events, as compared to placebo. The cohort enrolled included those with eGFR under 60 ml/min/1.73 m^2, age greater than 40 years, and was an international study including more than 9000 subjects from around the globe. The lipid-lowering strategy was effective and safe. Lipid targets have not been established specifically for people with CKD. Treatment strategies should be implemented in accordance with current recommendations for high-risk populations.

At the time of this writing, the *KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease* was under preparation for public review. In brief, the key aspects of the draft recommendations include treating those at high risk for atherosclerotic disease with lipid-lowering therapies, regardless of LDL levels, in those 50 years of age and above. Since this Guideline has not yet been finalized, interested readers should refer to the final document when it is formally released in 2013.

The benefits of aspirin in people with CKD and hypertension was demonstrated in a *post hoc* analysis of the Hypertension Optimal Treatment (HOT) trial.[450] Jardine et al. reported that among every 1000 persons with eGFR <45 ml/min/1.73 m^2 treated for 3.8 years, 76 major cardiovascular events and 54 all-cause deaths will be prevented while 27 excess major bleeds will occur. They concluded that an increased risk of major bleeding appears to be outweighed by the substantial benefits. Clopidogrel is used as an alternative to aspirin but CKD has been shown to be associated with an increase in platelet reactivity and there is resistance to clopidogrel in people with CKD, diabetes, and CVD.[451] The Clopidogrel for Reduction of Events During Observation (CREDO) trial concluded that clopidogrel in mild or moderate CKD may not have the same beneficial effect as it does in people without CKD. Subjects with normal renal function who received 1 year of clopidogrel had a marked reduction in death, MI, or stroke compared with those who received placebo (10.4% versus 4.4%, $P < 0.001$), whereas those with mild and moderate CKD did not have a significant difference in outcomes with clopidogrel therapy versus placebo (mild: 12.8% versus 10.3%, $P = 0.30$; moderate: 13.1% versus 17.8%, $P = 0.24$). Clopidogrel use was associated with an increased RR of major or minor bleeding, but this increased risk was not different based on renal function.[452]

International Relevance

Although it is clear and mentioned in many guidelines that CKD is associated with an increase in CVD risk, it is not included in many assessment tools and there is a deficiency in ethnicity and regional specific tools.

The assessment tool from US Third Report of the National Cholesterol Education Program (NCEP III) does not include CKD. The Fourth Joint Task Force of the European Society of Cardiology suggest that both an eGFR of less than 60 ml/min/1.73 m^2 and albuminuria increase risk but do not quantify the risk or include CKD in their Systematic COronary Risk Evaluation (SCORE) assessment tool.[453] In the UK, the QRISK®2 online tool includes CKD as 'yes' or 'no' and therefore does not allow for level of eGFR or proteinuria.[454] The Joint British Societies Guidelines regards proteinuria as a sign of target organ damage, which conveys a risk of at least 20% in 10 years.[455]

A study of cardiovascular risk estimation in Chinese adults in the USA–People's Republic of China Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology (USA-PRC Study) did not include CKD as a risk factor at all.[456] It is also important to remember that in this population stroke was the predominant CVD. A review of 25 risk assessment tools identified only 2 derived from an Asian population.[457] However, links between GFR categories and CVD events are evident in the Asian population, for example in the Japanese Gonryo study.[458] A prospective study in a general Japanese population demonstrated links between lower GFR, high creatinine levels, and proteinuria with cardiovascular mortality particularly stroke.[459] In Chinese patients who were at least 50 years old and either had existing CVD or were at high risk, 34% had an eGFR <60 ml/min/1.73 m^2 and eGFR <45 ml/min/1.73 m^2 was found to be an independent predictor of all-cause and cardiovascular death.[460] In a population-based study of 2353 people aged over 40 years in Beijing, an eGFR

<90 ml/min/1.73 m^2 was associated with increased CVD risk, and for each CKD category stroke was more prevalent than MI.[461]

In India the increasing prevalence of type 2 diabetes is driving an increase in CKD and both are associated with increased cardiovascular risk. In CKD patients attending one clinic in North India, 28% had diabetes, 27% were overweight, and 92% had hypertension. Metabolic syndrome as defined by the International Diabetes Federation (IDF) 2007 guidelines was present in 39% and more frequent in women.[462]

Implications for Clinical Practice and Public Policy

A full CVD risk assessment in a person with CKD should include an estimate of GFR and a quantitative assessment of albuminuria. Cystatin C may be helpful at risk stratifying those at intermediate risk.

The key aspect of these recommendations is to ensure that people with CKD are not deprived of treatment strategies known to be effective in general populations.

Areas of Controversy, Confusion, or Non-consensus

Many of the traditional cardiovascular risk assessment tools do not adjust for the presence of early CKD. Any tool should also adjust for level of eGFR because of increasing risk associated with lower levels of kidney function. The Framingham risk equation underestimates true events in a CKD population, but no validated different tools exist at present which better quantify cardiovascular or mortality risk in CKD populations.

Proteinuria is considered to be a sign of target organ damage and thus associated with high cardiovascular risk. However, assessment of risk should also include the presence of albuminuria. Few studies exist which demonstrate that targeting lowering of proteinuria results in reduced cardiovascular risk, though a number of studies which have targeted interruption of the RAAS (and in which lowering of urine protein has also been shown) have demonstrated a benefit.

An appropriate risk assessment tool should be available to assess risk in people with CKD. Addition of the presence of CKD to conventional risk factors in the Reykjavik population increased discrimination but did not increase risk to the same degree as smoking or diabetes.[463] In the Framingham Heart Study, GFR category 3b (GFR 30–44 ml/min/1.73 m^2) was associated with CVD but not equivalent to previous CVD.[464]

Lifestyle modification has not been studied in large trials in people with CKD but smoking cessation, achievement of optimum weight, regular exercise, and salt restriction should be seen as reasonable aims.

Pediatric Considerations

It is presently unclear whether children with CKD and elevated lipid levels will benefit from lipid-lowering strategies with no prospective trials ongoing in this area. It is hoped that data from both CKiD[55] and the 4C trials[78] may be able to address these shortcomings.

However, given that these children demonstrably have elevated risk of cardiovascular and atherosclerotic disease (see Recommendation 4.1.1), that there are data supporting the use of a number of statins in the pediatric population,[465] and that the adult evidence for benefit of statins in a subset of the SHARP trial[449] with a GFR <60 ml/min/1.73 m^2 exist, it would seem reasonable to consider the use of such drugs in children with CKD and elevated lipids.

Recommendations from 2006[441] for use of dietary modifications, followed by statins in children older than 8 years of age with persistent elevation in LDL-C levels, have been endorsed by the American Academy of Pediatrics. However, at the time of publication of these guidelines, the KDIGO Dyslipidemia Work Group has suggested that statin therapy may not be appropriate.

Age- and renal function-adjusted doses of such drugs should be carefully considered prior to any therapy being initiated (see Recommendation 4.4.1).

Regarding diabetes control, treatment in keeping with national and international diabetes recommendations is prudent. Note is made that there are specific caveats with respect to drugs and side effects that are important (see Recommendations 3.1.15-3.1.18).

There is no literature in the area of antiplatelet agents in atherosclerotic disease in the subset of children with CKD and the suggestion to offer antiplatelet agents does not apply to pediatric practice.

4.1.4: We suggest that the level of care for heart failure offered to people with CKD should be the same as is offered to those without CKD. (*2A*)

4.1.5: In people with CKD and heart failure, any escalation in therapy and/or clinical deterioration should prompt monitoring of eGFR and serum potassium concentration. (*Not Graded*)

RATIONALE

This statement is worded this way to make clinicians aware that people with CKD and heart failure should receive at least equal benefit from heart failure therapy as those without CKD, but that heart failure therapies (in particular increase of RAAS blockade and diuretic therapy) may lead to significant changes in GFR and serum potassium concentrations. This does not imply that such therapy should be avoided but only that clinicians are cognizant of this possibility, monitor it, and understand it in the context of individual risks and benefits.

Heart failure is a complex clinical syndrome which can be caused by any structural or functional cardiac disorder that impairs the pump function of the heart and has a high mortality. Within the general population, the commonest causes of heart failure are ischemic heart disease causing left ventricular systolic dysfunction, and hypertensive heart disease with left ventricular hypertrophy and diastolic dysfunction. Thus people with CKD are at increased risk of both. Evidence-based medication for heart failure impacts on

GFR and prescribers need to be alert to this. Changes in GFR are often transient and the downward trajectory GFR is not sustained if all other aspects of care and clinical status are stable. Monitoring and close follow-up are required.

Evidence Base

In an outpatient setting, normal GFR is unusual in heart failure. A study from the Alberta Heart Function Clinic found that in people with an ejection fraction of $\leq$35%, GFR categories G3a and G3b (GFR 30–59 ml/min/1.73 m^2) were present in 40% and 16% of people were GFR categories G4 or G5 (GFR $<$ 30 ml/min/1.73 m^2).[466] This study demonstrated a 1% increase in mortality associated with each 1 ml/min fall in CrCl demonstrating the clear link between kidney function and outcome for people with CKD and heart failure. Meta-analysis of 16 studies and over 80,000 people with heart failure by Smith et al. showed that renal impairment was present in 63% and was associated with increased mortality across the range of kidney function, with an adjusted HR of 1.56 (95% CI 1.53-1.60).[467] In the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) Program with candesartan in heart failure, 36% of subjects had eGFR $<$60 ml/min/1.73 m^2 which was associated with increased mortality and hospital admission regardless of ejection fraction.[468] The Digitalis Intervention Group (DIG) identified a GFR of 50 ml/min as a risk threshold for increased mortality risk in heart failure.[469] Smith et al. demonstrated that 1-year mortality after admission for heart failure was 29% in people with normal kidney function but 52% in those with moderate to severe renal impairment.[470] Anand et al. also demonstrated an independent association between the presence of positive reagent strip proteinuria present in 8% of subjects and increased mortality in heart failure.[471]

In the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) study of people with heart failure related to coronary artery disease (CAD), 39% had CrCl $<$60 ml/min ($<$1 ml/s). This study also demonstrated that the level of kidney function was a better indicator of poor outcome than cardiac anatomy.[472] In people admitted to hospital with heart failure, increasing SCr concentration is associated with a longer hospital stay and worse outcome.[473]

LVH is present in 40% of people with CKD,[474] progressively increasing as kidney function declines.[475] Ha et al. demonstrated LVH in 87% of people with predialysis CKD.[476] Parfrey et al. in a study of 432 people who were predialysis, found that only 16% had a normal echocardiogram while 41% had concentric LVH, 16% systolic dysfunction, and 28% left ventricular dilatation.[477] LVH is related to increased work load caused by arterial stiffness and hypertension, and at lower levels of GFR, volume overload. Alterations in electrolyte balance, anemia, bone metabolism, uremia, oxidative stress, inflammation, and other inflammatory mechanisms all play a role.[478]

In the majority of people with CKD, the myocardium develops concentric hypertrophy[476] with interstitial fibrosis and CKD-associated cardiomyopathy, leading to left ventricular stiffness.[474] This results in diastolic heart failure; people with CKD have higher mortality from diastolic heart failure than systolic heart failure.[479] Diastolic heart failure is more common in people with CKD who are older females with hypertension and/or diabetes.[480]

Left ventricular hypertrophy is particularly associated with anemia and a fall in Hb to less than 12.8 g/dl (128 g/l) is associated with left ventricular growth in people with early CKD.[481] Lower Hb levels are associated with increased risk of death and hospitalization in heart failure.[482] Other cardiovascular conditions, for example MI and atrial fibrillation, are more common in CKD and may exacerbate heart failure.

It is important to note that in a study of an older population (age $>$64 years), heart failure was an independent predictor of rapid kidney function decline.[483]

Standard therapy for the management of systolic heart failure includes an ACE-I or ARB and a beta-blocker licensed for heart failure such as bisoprolol or carvedilol. Meta-analysis of 25 trials of RAAS blockade (ACE-I or ARB) in people with CKD or proteinuria, demonstrated a reduction in the risk for heart failure and reduction in cardiovascular outcomes.[484] Subgroup analysis from the Valsartan Heart Failure Trial (Val-HeFT) demonstrated the beneficial effect of valsartan in people with CKD and that valsartan reduced the eGFR by the same amount in people with and without CKD.[471] Candesartan was also clinically effective in the CHARM study regardless of underlying kidney function[468] while irbesartan was associated with a 23% reduction in hospital admissions related to heart failure in people with nephropathy due to type 2 diabetes.[485] Analysis of data on bisoprolol from the Cardiac Insufficiency Bisoprolol Study II (CIBIS II)[486] identified 32% of subjects with eGFR $<$60 ml/min/1.73 m^2. These subjects were more likely to die or be admitted to hospital than those with eGFR $\geq$60 ml/min/1.73 m^2. However, they showed a similar benefit from bisoprolol treatment. A *post hoc* analysis of data on carvedilol from the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) and Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trials identified 60.8% of participants with eGFR $<$60 ml/min/1.73 m^2.[487] Carvedilol was well tolerated by subjects with CKD, and decreased all-cause, cardiovascular, and heart failure mortality. However, doubts were raised over the benefits when eGFR $<$45 ml/min/1.73 m^2.

Aldosterone antagonists are included in standard heart failure management, usually in addition to an ACE-I or ARB, leading to concerns relating to risk of hyperkalemia, particularly in people with lower GFRs. In a study of spironolactone therapy in severe heart failure, Pitt et al.[488] included subjects with SCr concentrations up to 2.5 mg/dl (221 μmol/l). There was a 30% reduction in mortality with spironolactone and the incidence of hyperkalemia was low. However, a review of real-world practice demonstrated a significant increase in hyperkalemia with the combination of RAAS blockade and an aldosterone antagonist, highlighting

the need for close monitoring with the introduction of combination therapy.[489]

In the APPROACH study on the specialist management of heart failure, subjects with CAD and CKD, despite being at high risk, were less likely to be taking ACE-Is, beta-blockers, statin, and aspirin. This study demonstrated that those subjects taking beta blockers had lower mortality, however ACE-Is were only of benefit when eGFR was >60 ml/min/1.73 m^2.[472]

International Relevance

The treatment of heart failure is similar around the globe. The ability to closely monitor kidney function or to offer conventional therapies may differ, however. Irrespective, this statement should hold true internationally. The National Heart Care Project of community subjects admitted to hospital with heart failure studied the differences between people of black and white ethnic groups. People with worse renal function were more likely to be black, older and female, and black people had a greater prevalence of hypertension and diabetes but less ischemic heart disease. Black people had a lower risk of mortality at every level of creatinine, for every 0.5 mg/dl (44.2 μmol/l) increase in creatinine, 1-year death risk increased 10% in black people and 15% in white people.[470]

Implications for Clinical Practice and Public Policy

Cardiorenal syndrome, an impairment of kidney function in the presence of heart disease, is a marker of worse prognosis. In addition to GFR, the presence and severity of albuminuria and anemia aid in prognostication and management.[490]

Where the link between LVH and heart failure in CKD is so strong and the outcome poor for people with LVH, efforts should be made to optimize care particularly BP. There is a lack of robust evidence for the optimal medical management of heart failure specifically in people with CKD; however, the prevalence of people with early CKD is so high in heart failure trials that we can apply standard treatment to these people. For those people with eGFR <45 ml/min/1.73 m^2, the situation is less clear.[487]

Areas of Controversy, Confusion, or Non-consensus

There are difficulties in making the diagnosis of heart failure in people with CKD, especially diastolic heart failure. Biomarkers such as B-type natriuretic peptide (BNP) may be abnormally elevated in CKD, but may or may not be as responsive to treatment or diagnostically accurate in people with CKD (see Chapter 4.2). There is little evidence to guide the management of left ventricular systolic dysfunction in people with CKD and evidence for the management of diastolic heart failure is generally lacking. However, there is evidence that medications to improve the outcome of people with heart failure are underused in people with CKD.

Appropriate management of the metabolic complications of kidney disease which can exacerbate heart failure needs to be clarified. Clinical studies are required on the role of device therapy in people with CKD (e.g., pacemakers, defibrillators, etc.).

4.2 CAVEATS WHEN INTERPRETING TESTS FOR CVD IN PEOPLE WITH CKD

BNP/N-terminal-proBNP (NT-proBNP)

As GFR diminishes, the prevalence and severity of cardiovascular abnormalities increase and are accepted as major causes of morbidity and mortality in people with CKD. The presence of congestive heart failure (CHF) in people with CKD conveys a worse prognosis than either condition alone. Therefore, early diagnosis and aggressive management of CHF are both highly desirable. A number of cardiac biomarkers (i.e., BNPs and cardiac troponins) appear to have both increasing clinical importance and increasing facility for detection and stratification of CHF. The stimulus for secretion of these biomarkers is the hemodynamic load (i.e., myocardial stretch) and their secretion is associated with the severity of CHF and the degree of left ventricular dysfunction. They are thus useful markers for diagnosis, management, and prognosis in people with normal renal function. However, when the eGFR is less than 60 ml/min/1.73 m^2, the accuracy of plasma BNP and NT-proBNP levels for detection and stratification of CHF becomes unreliable and the degree of responsiveness to treatment is not known.

4.2.1: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5), we recommend that serum concentrations of BNP/NT-proBNP be interpreted with caution and in relation to GFR with respect to diagnosis of heart failure and assessment of volume status. (*1B*)

RATIONALE

This statement is intended to remind clinicians that although the prevalence of fluid overload and heart failure increases with lower GFR categories, BNP becomes less reliable as a predictor of fluid overload and heart failure at lower GFRs. While it is associated with worse outcomes, cutoff values indicative of heart failure in general populations may or may not be appropriate and changes in values with treatment may or may not have the same meaning.

Evidence Base

Natriuretic peptides belong to a family of circulatory peptide hormones from either myocardial cell origin (atrial natriuretic peptide [ANP] and BNP) or endothelial cell origin (C-type).[491,492] They play an important role in regulating BP and body fluid volume by their natriuretic and diuretic actions, arterial dilatation, and inhibition of the RAAS.[493] Natriuretic peptides for the diagnosis of CHF have been a diagnostic breakthrough in cardiology where determination of their concentration in serum can help identify patients with left ventricular systolic dysfunction.[494,495]

Concentrations of natriuretic peptides increase in people with CHF and other CVDs as a consequence of

pressure and volume overload.[496,497] Among people with progressive LVH, concentrations of NT-proBNP are typically elevated in proportion to the degree of left ventricular mass increase.

Overall, BNP levels provide a better index of left ventricular mass and load than do ANP levels and BNP has emerged as a superior biomarker to ANP for clinical applications involving CHF and left ventricular dysfunction.[491,498] NT-proBNP may have analytical advantages over BNP because of greater stability due to a longer half-life. The cause of an elevated BNP level is multifactorial in origin and may reflect cardiac dysfunction, and/or changes in renal function.[499] Since renal dysfunction intrinsically was shown to affect BNP levels in some studies, the diagnostic value of BNP levels in the presence of CKD has been questioned.[500,501]

Earlier research hypothesized that measurement of natriuretic peptides could be of use in monitoring excess fluid volume and dry weight in people requiring dialysis,[502,503] but this remains unproven and the significance of plasma natriuretic peptides and their clinical role in dialysis remains unclear.[491]

Although several studies revealed higher BNP levels as GFR declined, outcomes of other studies suggest that the relationship between renal function and BNP levels may be most strongly dependent on cardiac and volume-related factors.[504–506] To test this hypothesis, Tagore et al. studied BNP levels in a cohort of 143 clinically euvolemic subjects with CKD in whom absence of heart disease was clinically validated and found that plasma BNP levels were independent of GFR.[504] Suresh and Farrington[507] studied people on dialysis and concluded that BNP levels were predictive of presence of left ventricular dysfunction, cardiac events, and survival in the presence of ESRD, suggesting that BNP levels may be informative across the full range of renal function and even in its absence. As previously established by several studies, the level of NT-proBNP is a strong prognostic marker in both the general population[508] and in various disease states, e.g., acute and CHF,[509,510] coronary heart disease,[511,512] and hypertension.[513]

International Relevance

The issue of how to differentially interpret BNP in the presence or absence of CHF and within the context of declining renal function has received considerable attention but remains incompletely resolved from a clinical perspective. Changes in either renal or cardiac function could potentially impact levels of natriuretic peptides and incomplete knowledge of an individual's clinical status relative to the degree of cardiac pathology or renal dysfunction could confound interpretation of BNP levels. Given the cost of biomarkers assays and the uncertainties related to interpretation of serum levels of BNP/NT-proBNP in people with CKD, competing priorities for health-care resource may dictate reliance on clinical evaluation and local practices of care in some areas of the world. Until better data are available, clinicians are asked to use this laboratory measurement with caution as a diagnostic test for heart failure in those with CKD.

Implications for Clinical Practice and Public Policy

Since people with ESRD with elevated levels of BNP have a higher RR of death, this biomarker could be used as an individual risk marker with the aim of identifying those at high risk. Clinical correlation is of utmost importance to ensure accurate diagnosis and appropriate therapy.

Studies to understand the variability of BNP by categories of eGFR and urine ACR, within and between individuals over time, and the response to therapy should be undertaken so as to better inform clinicians.

Areas of Controversy, Confusion, or Non-consensus

The relationship between renal function and BNP, the role of natriuretic peptides as markers of fluid overload and as predictors of mortality, and the utility of serial monitoring of BNP/NT-proBNP levels in people with CKD, and responsiveness to therapy remains unknown.

Clarification of issues and key points

Natriuretic peptides may be surrogate markers for prediction of mortality in people with CKD reflecting the association of mortality with left ventricular dysfunction and LVH. Before routine measurements of these biomarkers are recommended, their utility in guiding or changing clinical practice should be assessed.

Pediatric Considerations

There is robust literature in both children and neonates regarding both the normative values of BNP[514] and its value in predicting outcomes of pediatric heart failure.[515] To date no studies in children specifically address the issue of reduced GFR in this population. However, application of similar principles would likely apply.

Troponins

In recent years newer markers of myocardial injury have been introduced into clinical practice.[516,517] Among these, cardiac troponins have proven to be specific markers of myocardial damage.[518,519] Cardiac troponins have been considered the gold standard biochemical test for diagnosis of myocardial damage because they have nearly absolute myocardial tissue specificity, as well as high sensitivity, thereby reflecting even microscopic zones of myocardial necrosis.[517,520] Furthermore, increasing evidence indicates that abnormal troponin measurements identify a subgroup of patients who have an increased risk of major cardiac events[519,521–525] and that measurement of cardiac troponin T (cTnT) prior to commencing renal replacement is a significant independent predictor of survival.[526] However, these markers are renally excreted and are often found to be elevated in people with CKD irrespective of specific symptomatology. Thus, there is uncertainty as to the clinical importance of their different

magnitudes of elevation in CKD. There are no data on 'expected' values of these markers in the context of CKD, or at different categories of GFR and albuminuria.

4.2.2: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5), we recommend that serum concentrations of troponin be interpreted with caution with respect to diagnosis of acute coronary syndrome. (*1B*)

RATIONALE

This statement is intended to remind clinicians that isolated elevated serum concentrations of troponin (in the absence of symptoms or electrocardiographic changes) may not necessarily portend a diagnosis of ACS at lower GFR categories. While there are data linking troponin elevations with poor outcomes, the specific implications for an individual in clinical practice are not clear. Hence, this statement simply cautions the clinician with respect to interpretation but does not suggest that the laboratory values are not of significance. In a patient with clinical symptoms suggestive for ischemic heart disease, an elevated cardiac troponin I (cTnI) is suggestive for ACS.

Evidence Base

cTnT and cTnI are low-molecular-weight proteins that form part of the troponin complex and are integral components of the myofibrillar contractile apparatus of the heart.[527] Loss of integrity of cardiac myocyte membranes causes release of cardiac troponins into the circulation, which can be detected by highly sensitive assays developed for cTnT and cTnI to diagnose ACS.[521] A potent stimulus for the release or production of natriuretic peptides is mechanical stretching,[528] whereas plasma cTnT specifically and sensitively reflects myocardial injury and is considered to be an index of irreversible myocardial change.[521] In addition, cTnT levels can predict multi-vessel CAD in people requiring dialysis.[529] However, the significance of screening people with CKD for CAD using these cardiac biomarkers is questionable[530] since increases in serum cardiac troponin concentration can occur in the absence of an ACS.[531]

Most studies[517,532–545] have focused on people with ESRD where increases in serum cTnT concentrations have been observed in 20%–90% of subjects[540] but generally much lower when cTnI was measured. Information about cardiac troponins and their relationship with comorbidity is sparse in people with CKD who are not receiving dialysis treatment.[526,527,546,547] Increased cardiac troponin concentrations may occur early in CKD, including GFR categories 30-59 ml/min/1.73 m^2, and more commonly as CKD advances.

Powerful prognostic data emerging from the dialysis population demonstrate that increased concentrations of cardiac troponins reflect either subclinical myocardial damage caused by silent ischemia or myocardial remodeling in the development of LVH.[539,542]

Increased levels of cTnT measured with the highly sensitive assay, well below the detection range of standard assays, have been shown to be associated with cardiac structural abnormalities including LVH (both left ventricular wall thickening and dilation) and left ventricular systolic dysfunction,[548] and to have a graded association with all-cause and CVD mortality independent of traditional risk factors, renal function, and levels of other biomarkers such as high sensitivity CRP and NT-proBNP.

These findings suggest that chronic elevation of troponin levels may be mediated to a greater extent by indices of heart failure (such as higher left ventricular mass, left ventricular dysfunction, or increased NT-proBNP levels) than indices of atherosclerosis or ischemia.[548]

International Relevance

The costs of these tests, the differing sensitivity of the assays available, the paucity of data in people with CKD, and the poor correlation of serum troponin levels with ACS in people with CKD should be weighed against competing local health-care priorities and resource before their introduction into routine clinical practice. Emphasis should be placed on the clinical context and local standard practices of care.

Implications for Clinical Practice and Public Policy

Troponin elevation may result from repeated episodes of clinically silent MI,[522,549] although CAD frequently underlies troponin elevation and increased cTnT is also frequently encountered in patients at low risk for CAD. Troponin elevations are as frequent in subjects without CAD as in those with known CAD[517,550–552] and in people with CKD, serial increasing cTn levels may be of greater utility for diagnosis of ACS. In the context of symptoms and signs of ACS, elevations of troponins should not be ignored nor incorrectly attributed to simply 'CKD.' Thus the importance of ordering the test for specific indications for those with CKD should be emphasized.

Areas of Controversy, Confusion, or Non-consensus

Information about cardiac troponins and their relationship with comorbidity is sparse in people with CKD who are not receiving dialysis treatment. Although elevated values for TnT are common in people with low GFR in the absence of ACS or CHF, the prevelance of elevated TnI in the absence of ACS or CHF in people with low GFR may be only 0.4-6% depending on the cutoff value chosen.[532]

Clarification of Issues and Key Points

As pointed out by Roberts et al.,[553] although management strategies in people without CKD based on these biomarkers are quite clear, in people with CKD it is not the case despite the strong data on the prognostic implications. These biochemical markers can only be useful if they are interpreted in the context of the clinical history and examination with consideration given as to what management is appropriate for each individual, and if a cardiovascular therapy that is effective in this population is identified or developed.[553] The importance of understanding and contextualizing elevations

in troponin values in CKD populations cannot be overstated: under-treatment in symptomatic individuals should be avoided, and better understanding of treatment strategies in those asymptomatic individuals is the focus of ongoing study.

Pediatric Considerations

While normative values exist for troponin in children,[554] its utility as a general screening marker for myocardial ischemia in pediatrics has recently been called into question,[555] and no data exist relating reduced renal function and troponin levels in children.

Non-invasive testing

Most studies of cardiac evaluation in people with CKD have involved candidates for kidney transplantation in order to identify existing cardiac conditions amenable to risk modification and to exclude people with short expected survival due to cardiac morbidity. Among the tests for cardiovascular assessment, coronary angiography is considered invasive, expensive, and associated with risks such as contrast-induced nephropathy and cholesterol embolism. When trying to detect CAD or predict future cardiovascular events in people with CKD, nuclear imaging modalities using thallium tracers have shown conflicting results, especially in the context of small vessel disease. Clinicians should be aware of the limitations of radionuclear testing as a screening tool for significant CAD given the limitations of the test. Exercise-dependent techniques are limited by poor exercise tolerance of many subjects and people with CKD frequently have cardiac evaluation performed with pharmacological agents.[556,557]

4.2.3: We recommend that people with CKD presenting with chest pain should be investigated for underlying cardiac disease and other disorders according to the same local practice for people without CKD (and subsequent treatment should be initiated similarly). (*1B*)

4.2.4: We suggest that clinicians are familiar with the limitations of non-invasive cardiac tests (e.g., exercise electrocardiography [ECG], nuclear imaging, echocardiography, etc.) in adults with CKD and interpret the results accordingly. (*2B*)

RATIONALE

These statements are worded in this way firstly because although people with CKD are at increased risk from cardiovascular events, observational study has shown that they are frequently discriminated against in terms of investigation and management of such events. Secondly, non-invasive cardiac tests have known additional limitations in people with CKD and such limitations and their consequences need to be clearly understood by health professionals caring for people with CKD.

Evidence Base

Noninvasive stress testing appears to be the most common first approach to cardiac evaluation of asymptomatic patients, prompted by diabetes, age and risk-factor burden. These tests include myocardial perfusion studies, stress echocardiography, and most recently, cardiac computed tomographic angiography. However, people with CKD are underrepresented in studies evaluating the diagnostic sensitivities and specificities of noninvasive tests. Exercise ECG is limited by lack of specificity of the ST-segment response and by inability of many people with CKD to exercise to a diagnostic workload.

These tests have imperfect sensitivity and specificity in people with CKD or, in the case of tomographic angiography, evaluation in this population is as yet unpublished.[556] CAD has been detected in a high proportion of people on long–term dialysis therapy. Studies describing associations of angiographic coronary stenosis with subsequent clinical events in people with ESRD, including those undergoing transplant evaluations, have reached inconsistent conclusions.[558–562]

Abnormalities on myocardial perfusion studies correlate well with the presence of CAD in the general population, with mean weighted sensitivity of 88% and mean weighted specificity of 74%.[563] The performance of myocardial perfusion studies in identifying CAD in people with CKD is more variable, with reported sensitivities and specificities in people with ESRD ranging from 37% to 90% and 40% to 90%, respectively.[564–567] Nonetheless, results from myocardial perfusion studies have prognostic value for cardiac events and mortality.[568,569] In a meta-analysis of 12 studies involving thallium-201 scintigraphy and dobutamine stress echocardiography, people with ESRD with inducible ischemia had approximately 6 times the risk of MI and 4 times the risk of cardiac death as those without inducible defects.[570] Moreover, subjects with fixed defects also had nearly 5 times the risk of cardiac death.

The prognostic value of myocardial perfusion studies has been shown with other perfusion tracers. For example, in a study of 126 people with ESRD who underwent technetium-99m myocardial perfusion studies as part of their pre-transplant assessment, the presence of a reversible defect was associated with 3 times the risk of post-transplant cardiac events (HR 3.1; 95% CI 1.1-18.2) and nearly twice the risk of death (HR 1.92; 95% CI 1.1-4.4) compared with normal test results.[571]

De Lima et al.[572] prospectively studied 126 renal transplant candidates clinically classified as moderate (age >50 years) or high (diabetes, extra cardiac vascular disease, or known CAD) coronary risk with myocardial perfusion studies, dobutamine stress echocardiography, and coronary angiography. Significant CAD, defined as greater than 70% stenosis in 1 or more major epicardial artery on angiography was found in 42% of the sample. After a median follow-up of 46 months, clinical risk stratification and coronary angiography predicted major cardiac events, but myocardial perfusion studies and dobutamine stress echocardiography did not.

Newer imaging techniques are under current evaluation but a review here is beyond the scope of this guideline; these

techniques include: stress myocardial perfusion single photon emission computed tomography (SPECT);[557,573–576] ^{18}F-BMS, a novel fluorine-based myocardial perfusion tracer;[557,577] and gated imaging using radio-labelled ammonia ($^{13}NH_3$).

International Relevance

People with CKD who are being investigated prior to transplantation should be assessed according to the national and international cardiology guidelines and taking into account local practice and availability of resource.

Implications for Clinical Practice and Public Policy

There is still a need for a safe, noninvasive, diagnostic modality that will allow stratification of cardiovascular risk among people with CKD. With the development of new imaging markers, it becomes difficult for clinicians to choose the imaging tests that can best aid clinical decisions for a given patient. Imaging methods should provide accuracy and precision at acceptable cost. Until advanced imaging techniques (e.g., cardiac MRI, positron emission tomography, cardiac computed tomography) are standardized, clinicians should rely on the most reliable and familiar techniques in their environment.[578]

Areas of Controversy, Confusion, or Non-consensus

Clinical and cost-effectiveness could be improved; cardiac evaluation in people with CKD should be based on data from clinical trials.

Clarification of Issues and Key Points

If cardiac evaluation is at present predominantly used for risk stratification and prognosis, in the future it may guide optimal therapy and monitor clinical progress.[557]

4.3 CKD AND PERIPHERAL ARTERIAL DISEASE

There is a strong link between CKD and peripheral arterial disease (PAD). Symptoms of PAD may only be present in a minority of people who have clinical evidence of PAD.[579] It is therefore important to measure ankle-brachial index and perform regular systematic assessment of the lower limbs of people at high risk of PAD to identify bruits, loss of pulses, cool pale extremities, delay in venous filling, and skin ulceration.[580]

4.3.1: We recommend that adults with CKD be regularly examined for signs of peripheral arterial disease and be considered for usual approaches to therapy. (*1B*)

4.3.2: We suggest that adults with CKD and diabetes are offered regular podiatric assessment. (*2A*)

RATIONALE

These statements are worded in this way in order to highlight the increased risk of PAD in people with CKD, particularly those with CKD and diabetes.

Evidence Base

The prevalence of PAD is common in people with CKD and it increases with lower levels of GFR (Table 31). PAD can be

Table 31 | Peripheral arterial disease and CKD

Study	Population	PAD definition	Outcome of interest
O'Hare et al.[585]	NHANES age 40+	ABI <0.9	24% prevalence in people with CKD and a CrCl of <60 ml/min ($<$ 1 ml/s) versus 3.7% in those with normal kidney function
O'Hare et al.[587]	HERS study, postmenopausal women with known CHD	PAD event rates (amputation, revascularization, or lumbar sympathectomy)	Incident PAD event rates were 0.55%, 0.92%, and 2.73% per year with CrCl 60, 30-59, and 30 ml/min/1.73 m^2, respectively
O'Hare et al.[586]	Cardiovascular Health Study, adults age 65+	Lower-extremity PAD procedure (bypass surgery, angioplasty, or amputation)	HR for PAD procedure 2.5 (95% CI 1.2-5.1) for highest quintile of cystatin C ($\geq$1.28 mg/l) versus lowest ($\leq$0.9 mg/l)
De Vinuesa et al.[582]	102 adults in a CKD clinic, mean age 70 $\pm$ 11 years, GFR 15-60 ml/min/1.73 m^2	ABI <0.9	17% signs and symptoms of PAD, which had passed unnoticed; 32% had ABI <0.9 (mean 0.64 ± 0.25)
Liew et al.[584]	6-year follow up of 1027 subjects (ABI index recording and GFR measured within 90 d)	ABI <0.9	6-year mortality rate for CKD and PAD 45% versus 28% CKD alone, 26% PAD alone, and 18% for neither condition
Wattanakit et al.[588]	6760 subjects, aged 45–84 years in the Multi-Ethnic Study of Atherosclerosis	ABI <0.9	Albuminuria was associated with PAD in subjects with diabetes (odds ratio 1.90, 95% CI 1.19–3.04) but not in those without
Lash et al.[583]	3612 subjects age 58.2 ± 11.0 years in the Chronic Renal Insufficiency Cohort study	ABI <0.9	Overall, 16% prevalence of PAD in subjects with GFR$<$60 ml/min/1.73 m^2, increasing from 4% in those with GFR$>$60 to 22% in those with GFR$<$30 ml/min/1.73 m^2
Bello et al.[581]	920,985 subjects with GFR and proteinuria assessment, median follow-up 35 months (IQR 22-44)	Time to first hospitalization with PAD	1891 of subjects (0.2%) hospitalized at least once for PVD, adjusted rates increased with lower GFR

Abbreviations: ABI, ankle-brachial index; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; d, day; GFR, glomerular filtration rate; HERS, Heart and Estrogen/Progestin Replacement Study; HR, hazard ratio; IQR, interquartile range; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral arterial disease; PVD, peripheral vascular disease.

attributed to the greater prevalence of traditional risk factors such as diabetes, hypertension, dyslipidemia, advanced age, and renal-specific factors.[581–588]

Diabetes is the leading cause of CKD globally and the risk of diabetic foot ulceration and lower extremity amputation in subjects with diabetes increases dramatically with lower GFR. In a cohort of 90,617 individuals with diabetes over a median observation time of 2.4 years, the HR for amputation increased from 2.08 (95% CI 1.68–2.58) for those with GFR 30-59 ml/min/1.73 m^2 to 7.71 (95% CI 5.29–11.26) for those with GFR <30 ml/min/1.73 m^2 compared to reference subjects with GFR >60 ml/min/1.73 m^2.[589]

Screening for PAD is recommended for adults in the general population based on age and number of risk factors.[590] Although an ankle-brachial index of <0.9 is generally considered evidence of PAD, the utility of this measure is unproven in CKD because of the greater prevalence of vessel calcification. Evidence-based medical therapies for PAD in people with CKD are similarly lacking. Smoking cessation is mandatory. Aspirin may be beneficial for prevention of cardiovascular events. Clopidogrel has not been studied in people with CKD and PAD. No RCTs evaluating percutaneous versus surgical revascularization techniques have been conducted in people with CKD and PAD but outcome studies all suggest that CKD confers an increased risk of adverse outcome, regardless of the revascularization technique employed.[591,592] These statements do not apply to pediatric practice.

International Relevance

There is no evidence to suggest that the international approach to identification and management of PAD in people with CKD should differ.

Implications for Clinical Practice and Public Policy

People with CKD are more at risk of PAD and need regular assessment and monitoring. The role of ankle-brachial index versus other diagnostic techniques may have implications for future practice. Prospective data on non-surgical therapies and data regarding percutaneous versus surgical revascularization are required to inform policy and recommended procedure.

Areas of Controversy, Confusion, or Non-consensus

There remains ongoing debate as to the timing and use of specific diagnostic criteria for identification of PAD in people with CKD and no studies have examined the utility of conventional methods in early detection of PAD in CKD. The use of specific medical and surgical management strategies in people with CKD and PAD has not been evaluated. There is no reason to believe that treatment strategies should differ, though risks of diagnostic testing (such as angiography) remain real.

4.4 MEDICATION MANAGEMENT AND PATIENT SAFETY IN CKD

Many drugs and investigative pharmaceuticals are renally excreted and their dosage may need to be reduced in patients with CKD in order to avoid toxicity. As many people with CKD are elderly, there should also be consideration of chronological age.

It is beyond the scope of this guideline to list all the agents that may need dose adjustment in CKD or which should be avoided due to potential nephrotoxicity. This information is widely available in documents which may exist at local, regional, or national bodies (e.g., British National Formulary: www.bnf.org), and other textbooks of pharmacology.[593,594] However key classes of commonly prescribed drugs in people with CKD will be mentioned together with suggestions for dose adjustment. Much of this guidance is based upon our understanding of pharmacology and pharmacokinetics rather than randomized control trial evidence.

The statements presented here are intended to inform clinicians caring for those with CKD or at risk for CKD with respect to common clinical situations or exposures which may put people at risk for AKI or progression of CKD.

4.4.1: We recommend that prescribers should take GFR into account when drug dosing. (*1A*)

4.4.2: Where precision is required for dosing (due to narrow therapeutic or toxic range) and/or estimates may be unreliable (e.g., due to low muscle mass), we recommend methods based upon cystatin C or direct measurement of GFR. (*1C*)

4.4.3: We recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include, but are not limited to: RAAS blockers (including ACE-Is, ARBs, aldosterone inhibitors, direct renin inhibitors), diuretics, NSAIDs, metformin, lithium, and digoxin. (*1C*)

4.4.4: We recommend that adults with CKD seek medical or pharmacist advice before using over-the-counter medicines or nutritional protein supplements. (*1B*)

4.4.5: We recommend not using herbal remedies in people with CKD. (*1B*)

4.4.6: We recommend that metformin be continued in people with GFR ≥ 45 ml/min/1.73 m^2 (GFR categories G1-G3a); its use should be reviewed in those with GFR 30–44 ml/min/1.73 m^2 (GFR category G3b); and it should be discontinued in people with GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5). (*1C*)

4.4.7: We recommend that all people taking potentially nephrotoxic agents such as lithium and calcineurin inhibitors should have their GFR, electrolytes and drug levels regularly monitored. (*1A*)

4.4.8: People with CKD should not be denied therapies for other conditions such as cancer but there should be appropriate dose adjustment of cytotoxic drugs according to knowledge of GFR. (*Not Graded*)

RATIONALE

These statements are worded in this way in order to inform appropriate prescribing and management of medical conditions in people with CKD. Recommendation 4.4.1 is specifically worded to ensure that clinicians remember that in those circumstances where accurate GFR is required (narrow therapeutic or toxic window), a direct measurement, not an estimate of GFR should be undertaken.

Evidence Base

Potential problems associated with use of medication in people with CKD include:

a) Reduced ability to excrete drugs and/or their metabolites
b) Increased sensitivity to medications (e.g., those bound to albumin in hypoalbuminemic states such as nephrotic syndrome)
c) Diminished tolerance of side effects, particularly in the elderly
d) Loss of efficacy[13]

Wherever possible, people with CKD should receive the same treatment as those with normal renal function. However, the dosages may need adjustment according to GFR.

There are medicines whose toxicity is worsened in acute illness particularly in a setting of dehydration such as diarrhea and vomiting. General advice about appropriate dosing and when to restart these agents should be given to people taking these drugs during intercurrent illness, together with a recommendation for consultation with a health-care professional as soon as possible.

Use of herbal and over-the-counter medicines is very common worldwide and some (such as those containing aristolochic acid)[595,596] are known to be nephrotoxic. There is no good quality safety or efficacy data for many of these compounds.

Table 32 details specific advice for various classes of drugs where CKD may be an issue. These include RAAS blocking agents,[262] beta-blockers, analgesics, antibiotics, lithium,[597] hypoglycemic agents,[598–600] lipid-lowering agents,[449,601–604] certain chemotherapeutic agents, and anticoagulants.[605]

International Relevance

This guidance is based upon knowledge of pharmacology that has universal relevance. The main international implication is centered on costs of some newer therapies compared to the older ones. Somewhat paradoxically, as the weight of evidence resides mainly with agents that have been available for longer, they have the advantage of being less costly, and have the side effects that are well documented; thus many of these older agents are preferred.

Pediatric Considerations

No specific recommendation for or against the use of a BSA adjusted eGFR in relation to drug dosing can be made in children with CKD as the majority of drug studies have been performed in adult males and extrapolated to children without consideration for BSA and/or pediatric renal function or clearance.

The exception to this rule would be that for any drug where pediatric pharmacokinetic or pharmacodynamic studies exist, the method used in calculating the effect of renal function should be used when estimating the need for dose adjustments or modifications for the individual patient.

Numerous resources for dose adjustments for pediatric CKD and ESRD patients exist, including those found in numerous textbooks[606,607] and online resources.[608]

An additional value of dedicated pediatric renal multidisciplinary teams, in terms of caring for children with CKD and ESRD, is their ability to provide anticipatory guidance for the patients and families. All such teams should at the least provide written or online information to their patients and families directing them to seek advice in situations where they may be prescribed medications from other providers or may be seeking over-the-counter drugs or supplements. The presence of trained pediatric pharmacists as part of such teams can be invaluable in achieving such support and education for both families as well as the CKD health-care providers and community resources such as local pharmacists.

LIMITATIONS

People with CKD are often excluded or not identified from trials of medications for non-renal disease. Recommendations are partly based upon knowledge of pharmacology rather than controlled trials in carefully defined populations.

RESEARCH RECOMMENDATIONS

National and international research groups, and those with CKD-focus organizations (International Society of Nephrology, International Federation of Kidney Foundations, and other national bodies) should ensure adequate representation of people with CKD in clinical trials, leading to an improved understanding of pharmacodynamics of those with CKD.

4.5: IMAGING STUDIES

4.5.1: Balance the risk of acute impairment in kidney function due to contrast agent use against the diagnostic value and therapeutic implications of the investigation. (*Not Graded*)

RATIONALE

Use of iodinated radiocontrast media has been associated with AKI with reported rates of 0-11% depending on the population under study, the type of agent that is used, and the definition of nephrotoxicity.[609] The following recommendations are concordant with those from the American College of Radiology (ACR),[610] the European Society of Urogenital Radiology (ESUR)[611] and the *KDIGO Clinical Practice Guideine for Acute Kidney Injury.*[7]

Table 32 | Cautionary notes for prescribing in people with CKD

Agents	Cautionary notes
1. Antihypertensives/cardiac medications	
RAAS antagonists (ACE-Is, ARBs, aldosterone antagonists, direct renin inhibitors)	• Avoid in people with suspected functional renal artery stenosis • Start at lower dose in people with GFR <45 ml/min/1.73 m^2 • Assess GFR and measure serum potassium within 1 week of starting or following any dose escalation • Temporarily suspend during intercurrent illness, planned IV radiocontrast administration, bowel preparation prior to colonoscopy, or prior to major surgery • Do not routinely discontinue in people with GFR <30 ml/min/1.73 m^2 as they remain nephroprotective
Beta-blockers	• Reduce dose by 50% in people with GFR <30 ml/min/1.73 m^2
Digoxin	• Reduce dose based on plasma concentrations
2. Analgesics	
NSAIDS	• Avoid in people with GFR <30 ml/min/1.73 m^2 • Prolonged therapy is not recommended in people with GFR <60 ml/min/1.73 m^2 • Should not be used in people taking lithium • Avoid in people taking RAAS blocking agents
Opioids	• Reduce dose when GFR <60 ml/min/1.73 m^2 • Use with caution in people with GFR <15 ml/min/1.73 m^2
3. Antimicrobials	
Penicillin	• Risk of crystalluria when GFR <15 ml/min/1.73 m^2 with high doses • Neurotoxicity with benzylpenicillin when GFR <15 ml/min/1.73 m^2 with high doses (maximum 6 g/day)
Aminoglycosides	• Reduce dose and/or increase dosage interval when GFR <60 ml/min/1.73 m^2 • Monitor serum levels (trough and peak) • Avoid concomitant ototoxic agents such as furosemide
Macrolides	• Reduce dose by 50% when GFR <30 ml/min/1.73 m^2
Fluoroquinolones	• Reduce dose by 50% when GFR <15 ml/min/1.73 m^2
Tetracyclines	• Reduce dose when GFR <45 ml/min/1.73 m^2; can exacerbate uremia
Antifungals	• Avoid amphotericin unless no alternative when GFR <60 ml/min/1.73 m^2 • Reduce maintenance dose of fluconazole by 50% when GFR <45 ml/min/1.73 m^2 • Reduce dose of flucytosine when GFR <60 ml/min/1.73 m^2
4. Hypoglycemics	
Sulfonylureas	• Avoid agents that are mainly renally excreted (e.g., glyburide/ glibenclamide) • Other agents that are mainly metabolized in the liver may need reduced dose when GFR <30 ml/min/1.73 m^2 (e.g., gliclazide, gliquidone)
Insulin	• Partly renally excreted and may need reduced dose when GFR <30 ml/min/1.73 m^2
Metformin	• Suggest avoid when GFR <30 ml/min/1.73 m^2, but consider risk-benefit if GFR is stable • Review use when GFR <45 ml/min/1.73 m^2 • Probably safe when GFR $\geqslant 45$ ml/min/1.73 m^2 • Suspend in people who become acutely unwell
5. Lipid-lowering	
Statins	• No increase in toxicity for simvastatin dosed at 20 mg per day or simvastatin 20 mg /ezetimide 10 mg combinations per day in people with GFR <30 ml/min/1.73 m^2 or on dialysis[449] • Other trials of statins in people with GFR <15 ml/min/1.73 m^2 or on dialysis also showed no excess toxicity
Fenofibrate	• Increases SCr by approximately 0.13 mg/dl (12 μmol/l)
6. Chemotherapeutic	
Cisplatin	• Reduce dose when GFR <60 ml/min/1.73 m^2 • Avoid when GFR <30 ml/min/1.73 m^2
Melphalan	• Reduce dose when GFR <60 ml/min/1.73 m^2
Methotrexate	• Reduce dose when GFR <60 ml/min/1.73 m^2 • Avoid if possible when GFR <15 ml/min/1.73 m^2
7. Anticoagulants	
Low-molecular-weight heparins	• Halve the dose when GFR <30 ml/min/1.73 m^2 • Consider switch to conventional heparin or alternatively monitor plasma anti-factor Xa in those at high risk for bleeding
Warfarin	• Increased risk of bleeding when GFR <30 ml/min/1.73 m^2 • Use lower doses and monitor closely when GFR <30 ml/min/1.73 m^2
8. Miscellaneous	
Lithium	• Nephrotoxic and may cause renal tubular dysfunction with prolonged use even at therapeutic levels • Monitor GFR, electrolytes, and lithium levels 6 monthly or more frequently if the dose changes or the patient is acutely unwell • Avoid using concomitant NSAIDs • Maintain hydration during intercurrent illness • Risk-benefit of drug in specific situation must be weighed

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine.

Radiocontrast

4.5.2: We recommend that all people with GFR <60 ml/min/1.73m^2 (GFR categories G3a-G5) undergoing elective investigation involving the intravascular administration of iodinated radiocontrast media should be managed according to the *KDIGO Clinical Practice Guideline for AKI* including:

- **Avoidance of high osmolar agents (*1B*);**
- **Use of lowest possible radiocontrast dose (*Not Graded*);**
- **Withdrawal of potentially nephrotoxic agents before and after the procedure (*1C*);**
- **Adequate hydration with saline before, during, and after the procedure (*1A*);**
- **Measurement of GFR 48–96 hours after the procedure (*1C*).**

RATIONALE

These statements have been worded in order to inform safe radiological investigation of people with CKD and to avoid potential nephrotoxcity that can be associated with radiological imaging.

Evidence Base

Radiocontrast media associated AKI is a largely preventable cause of morbidity and mortality. There is no internationally agreed definition but most studies use an increase in SCr of >0.5 mg/dl (44 μmol/l) and/or a 25% increase from baseline SCr within 3 days of the procedure.[7,609–611] Epidemiological studies and case series have identified the following risk factors for AKI:

a) GFR <60 ml/min/1.73 m^2 (particularly if <30 ml/min/1.73 m^2)
b) Diabetes
c) Concurrent dehydration
d) CHF
e) >70 years of age
f) Concurrent use of known nephrotoxic agents such as NSAIDs
g) Use of high osmolality agents (especially in those with GFR <60 ml/min/1.73 m^2)
h) Use of large doses of radiocontrast media
i) Intra-arterial injection
j) Gout (hyperuricemia)

Numerous studies of preventative strategies have been performed with the following conclusions:

a) High osmolar agents pose a greater risk of AKI in people with CKD.[609]
b) Iso-osmolar agents compared to low-osmolar agents are associated with lower rates of AKI in some but not all studies. Wherever possible iso-osmolar agents should be used in people with CKD at high risk for AKI (although these tend to be more expensive).[612]
c) Although risk for AKI increases with GFR <60 ml/min/1.73 m^2, the rates are particularly high (7.8% in one study) when GFR is <30 ml/min/1.73 m^2. Implementing preventative strategies for all with a GFR <60 ml/min/1.73 m^2 may not be practical but a graded risk assessment taking into account all factors may be more realistic. Some guidelines such as American College Radiology[610] and ESUR[611] provide a checklist as a means of identifying patients at risk of AKI before investigation.
d) Extracellular volume expansion is widely recommended although there are few good quality trials on which to base an ideal protocol.[609] 0.9% saline given by continuous infusion appears superior to 0.45% saline or bolus injection and there is no demonstration of consistent superiority of sodium bicarbonate over saline. Current guidance suggests either infusion of 1 ml/kg body weight/hour for 3-12 hours before and after the procedure or 100 ml/hr, beginning 6 to 12 hours before and continuing 4 to 12 hours after intravascular iodinated contrast medium administration.[609,610]
e) Use of N-acetylcysteine or ascorbic acid as preventative measures has not been shown to be a consistent benefit.

International Relevance

This guidance has universal relevance although there are cost implications as the iso-osmolar contrast media are more expensive.

LIMITATIONS

Some of the guidance is based upon limited evidence and there is a need for more research into simple preventative measure such as pre-investigation rehydration (see below). There has not previously been a universal definition for AKI following administration of contrast media. However, recommendations from the KDIGO AKI Guideline suggest that the same general AKI definition and staging be used for changes in kidney function, irrespective of etiology.

RESEARCH RECOMMENDATIONS

Prospective studies using direct measures of GFR before and after administration of radiological contrast media are required to help define the incidence of AKI. Such studies would also be able to validate creatinine or other estimates of GFR in people undergoing radiological investigation.

Prospective controlled trials of rehydration using different fluids (saline, bicarbonate, Hartmann's) and validated estimates of GFR are urgently required.

Definitive studies of N-acetylcysteine and other antioxidants would help determine their usefulness or otherwise.

Gadolinium-containing contrast media

Gadolinium is a rare earth element that is naturally highly toxic. When bound to proprietary chelating agents, it is essentially biologically inert in people with normal renal function and provides excellent contrast during MRI. These

chelates are excreted unchanged by the kidneys by glomerular filtration and have much lower direct nephrotoxicity than conventional radioiodine contrast media.[613] However over 200 cases of a scleroderma-like condition now termed nephrogenic systemic fibrosis (NSF) following gadolinium use in patients with CKD have been reported.[613, 614]

4.5.3: We recommend not using gadolinium-containing contrast media in people with GFR <15 ml/min/1.73 m^2 (GFR category G5) unless there is no alternative appropriate test. (*1B*)

4.5.4: We suggest that people with a GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) who require gadolinium-containing contrast media are preferentially offered a macrocyclic chelate preparation. (*2B*)

RATIONALE

These statements have been worded in order to enable safe administration of gadolinium to people with CKD. As with all tests requested in the CKD population, clinicians should be aware of the risk-benefit ratio of the use of gadolinium in people with GFR 15-29 ml/min/1.73 m^2.

Evidence Base

NSF is an untreatable and sometimes fatal condition that complicates the use of gadolinium-containing contrast media in people with CKD. Prevention is therefore the best approach with avoidance of gadolinium exposure unless clinically indicated and to use the lowest risk agent at the lowest dose.[613,615]

Although the risk of AKI with iodinated contrast media is much greater than that for NSF with gadolinium, the former is treatable with dialysis whereas the latter is not. Thus, consideration of more conventional imaging techniques should be undertaken in all with a GFR <30 ml/min/1.73 m^2.[610,613–615]

A recent meta-analysis and review have highlighted those patients most at risk and quantified an OR for NSF of between 20-50 for those with a GFR <15 ml/min/1.73 m^2.[614]

While there is general agreement that patients with a GFR >15 ml/min/1.73 m^2 are at increased risk, it is not possible to derive a precise estimate. No patients with a GFR >30 ml/min/1.73 m^2 have developed NSF without concomitant liver failure.[614]

There is some suggestion that the type of gadolinium preparation plays a role:[614,615] Linear chelated preparations such as gadodiamide may be more likely to cause NSF and should be avoided when GFR is <30 ml/min/1.73 m^2. Gadoteridol, gadobutrol, or gadoterate should be considered if MRI with contrast is clinically essential.[610,613,615] Moreover, as gadolinium is freely dialysed,[616] most guidelines recommend dialysis in patients with a GFR <15 ml/min/1.73 m^2 or for those already on dialysis immediately after (and perhaps repeated 24 hours later) completion of the procedure.[610,615] The role of dialysis in people with GFR above 15 ml/min/1.73 m^2 is uncertain.

International Relevance

This guidance has universal relevance although there are cost implications as the non-linear chelated preparations are more expensive.

Pediatric Considerations

Regarding both Recommendations 4.5.3 and 4.5.4, a number of considerations specific to the use of gadolinium preparations in young children and neonates must also be considered in addition to the general admonishments against their use in situations of GFR <30 ml/min/1.73 m^2. In particular, the FDA currently does not license any gadolinium-based contrast agent (GBCA) product for use in children less than 2 years of age; and likewise the European Medicines Agency cautions against the use of any GBCA in a child less than 1 year of age.

In addition, the ability to accurately estimate the relative value of a neonate or young infant's GFR leads to great difficulty in terms of assigning risk of GBCA exposure if one bases this on renal clearance. In a recent paper by Meng and colleagues,[617] they surveyed a worldwide group of both cardiologists and radiologists with respect to their use of gadolinium in their pediatric MRI practice. While 93% of the respondents did evaluate renal function in some or all of their patients, only a slight majority (54%) used an estimating formula, most often the Schwartz equation, with the remainder relying on SCr alone (31%) or urine output (6%). Perhaps of most concern was that renal function was assessed in only 33% and 31%, respectively, of patients classified as 'all neonates' or 'all patients <1 week of age.' Equally concerning was the fact that 13% of the respondents would give gadolinium to some of these children in the face of a GFR <30 ml/min/1.73 m^2.

In recognition of our inability to accurately measure GFR in the neonate and, by extension, the clearance of compounds such as gadolinium, all nephrologists and radiologists must exercise caution in terms of use of GBCA in this potentially high-risk population, and all other imaging modalities should be considered prior to choosing one requiring gadolinium exposure.

LIMITATIONS

The evidence is largely based upon case series rather than prospective studies or RCTs.

RESEARCH RECOMMENDATIONS

As for iodinated contrast media, a prospective study of people with CKD undergoing nuclear MRI with gadolinium contrast would help define change in GFR and validate estimators. Because NSF is such a serious condition, an RCT of dialysis in people with GFR <30 ml/min/1.73 m^2 would help to determine risk-benefit in these patients, though recruitment may be difficult due to potential ethical concerns.

Bowel preparation

The increasing use of colonoscopy as a screening tool for bowel cancer has resulted in many people undergoing bowel

preparation with oral sodium phosphate-containing preparations. Case reports of acute and late irreversible renal failure with biopsy-proven phosphate deposition have led to a new disease entity termed acute phosphate nephropathy.[618,619] Less than 40 definite cases have been reported and these have been extensively reviewed.

4.5.5: We recommend not to use oral phosphate-containing bowel preparations in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) or in those known to be at risk of phosphate nephropathy. (*1A*)

RATIONALE

This statement has been worded in order to enable safe bowel preparation in people with CKD who need to undergo investigation of bowel disease.

Evidence Base

Electrolyte disturbances that are sometimes severe and include hyperphosphatemia, hypocalcemia, hypo- and hypernatremia, and hypokalemia have been reported in normal volunteers undergoing oral phosphate bowel preparation.[620] Renal injury has been reported in a small number of people although the condition is likely to be underrecorded. A recent study from Iceland estimated the incidence to be around 1 per thousand doses[621] but others would suggest incidence rates of between 1% and 4%.[618,619]

Two broad patterns of renal injury have been described. An early symptomatic response associated with severe hyperphosphatemia and hypocalcemia and a later (days to months) irreversible kidney injury associated with a specific tubulointerstitial calcium phosphate deposition.[618,619]

The following people are said to be at particular risk although the link to kidney injury is associative in many cases and firm evidence is lacking:

a) GFR <60 ml/min/1.73 m^2
b) >60 years of age
c) Female
d) Hypertension
e) Diabetes
f) CHF
g) Dehydration
h) Active colitis
i) Concurrent use of RAAS blocking agents, diuretics, lithium, NSAIDs
j) Large and/or repeat dosing of oral phosphate preparations
k) Hypoparathyroidism

Although the FDA has banned oral phosphate solutions, there is no qualitative difference with tablet preparations. Both should be avoided in people at risk and this is the current recommendation of the American Society for Gastrointestinal Endoscopy.[622]

There is some debate as to whether the cause of the kidney injury is entirely due to dehydration rather than phosphate use *per se*.[623] However, it is hard to understand why calcium phosphate deposits occur and cause late renal impairment if dehydration was the only factor.

There is a single RCT of phosphate versus non-phosphate preparations but assessment of renal function was limited to change in SCr and GFR at baseline is not reported.[624] Notwithstanding these limitations, there were greater changes in serum potassium, calcium, and phosphate in those given sodium phosphate-containing preparations.

As there are non-phosphate-containing bowel preparations available, these should be used in all the above groups (and arguably in all people given the biochemical abnormalities observed in normal volunteers). As for radiocontrast media, rehydration with saline may be required in the frail and ill irrespective of the bowel preparation that is used.

International Relevance

This guidance has universal relevance but non-phosphate-containing bowel preparations are more expensive, so the use of these agents may differ around the world.

LIMITATIONS

The data are based upon case series with a limited number of affected individuals and retrospective population studies.

RESEARCH RECOMMENDATIONS

Prospective study in people with normal renal function and those with different severities of CKD are urgently required in order to define the acute biochemical and metabolic effects of phosphate-containing bowel preparations. There is also a need for a study of all people undergoing bowel preparation with whatever preparation in order to explore the effects on GFR on the incidence of this complication. More definitive exploration of rehydration therapy (type and volume) in people with CKD undergoing bowel preparation is urgently needed.

4.6 CKD AND RISKS FOR INFECTIONS, AKI, HOSPITALIZATIONS, AND MORTALITY

The following section gives guidance for the care of people with CKD given that they are at increased risk for a number of events such as infections, AKI, CVD, hospitalizations, and mortality. Appreciating that increased risk and implementing some of the recommendations below may result in improved outcomes for people. It will be important to develop policies and robust research agendas to address areas which do not have a substantial evidentiary base.

CKD and risk of infections

CKD is associated with significant major infectious complications, which occur at rates 3 to 4 times the general population. Infection is an important cause of morbidity and mortality among patients with kidney failure and is the

second leading cause of death following CVD. CKD may be a risk-multiplier for acute infectious disease-associated mortality, as it is for CVD. Despite a less effective response to vaccination, there are data suggesting benefit from immunization among people with CKD as in the general population.

4.6.1: We recommend that all adults with CKD are offered annual vaccination with influenza vaccine, unless contraindicated. (*1B*)

4.6.2: We recommend that all adults with eGFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) and those at high risk of pneumococcal infection (e.g., nephrotic syndrome, diabetes, or those receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated. (*1B*)

4.6.3: We recommend that all adults with CKD who have received pneumococcal vaccination are offered revaccination within 5 years. (*1B*)

4.6.4: We recommend that all adults who are at high risk of progression of CKD and have GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) be immunized against hepatitis B and the response confirmed by appropriate serological testing. (*1B*)

4.6.5: Consideration of live vaccine should include an appreciation of the patient's immune status and should be in line with recommendations from official or governmental bodies. (*Not Graded*)

4.6.6: Pediatric immunization schedules should be followed according to official international and regional recommedations for children with CKD. (*Not Graded*)

RATIONALE

CKD is associated with alterations in primary host defense mechanisms and increases the risk of bacterial infections (Table 33). Epidemiological study suggests that the 3 most commonly seen infectious complications in the CKD population are: urinary tract infection, pneumonia, and sepsis. In the general population, there is strong evidence that preventive measures are effective in adults and there are data suggesting benefit from immunization in people with CKD.

Evidence Base

Previous investigations have firmly established ESRD as a strong risk factor for infectious complications.[625–628] However, few epidemiologic reports have addressed the risk of infections in people with CKD not treated with dialysis.[629,630] Data from the US Renal Data System (USRDS) suggest that higher rates of hospital admission because of septicemia are noted in people with CKD compared with those without CKD.[631] Comprehensive studies of the absolute rates, risk factors, clinical course, and outcomes of different types of clinically relevant infections across the spectrum of CKD are not available.

Among people with CKD, very few studies have examined the incidence or prevalence of infections and no published data describe GFR category–specific infection rates. Among Medicare beneficiaries aged more than 66 yr, people with diagnosed CKD seem to have substantially higher rates of hospitalization for diagnoses of pneumonia and sepsis compared with people without diagnosed CKD.[628] In addition to an increased incidence of being hospitalized with infections, people with CKD have longer lengths of hospital stay during infection-related admissions compared with people without CKD.[632]

Table 33 | Risk factors for infection in people with CKD

Advanced age
High burden of coexisting illnesses such as diabetes
Hypoalbuminemia[625]
Immunosuppressive therapy[628]
Nephrotic syndrome[634]
Uremia
Anemia and malnutrition[635]
High prevalence of functional disabilities

Abbreviation: CKD, chronic kidney disese

Among USRDS data admission rates for all causes, CVD and infection, are 38–46% higher for those with CKD than for those without.[633] Rates for pneumonia in CKD were nearly three times higher than those for non-CKD. Hospitalizations for bacteremia/septicemia, were nearly four times higher for people with CKD compared to those without. Hospitalization rates for urinary tract infections were three-fold higher for people with CKD.

In people with ESRD, the function of polymorphonuclear white blood cells, lymphocytes, and monocytes is altered, resulting in an impaired host response to infection.[636–638] However, these issues have not been adequately investigated in people with CKD.

There is a growing body of evidence in the general population for reduction in infections, hospitalizations, and mortality as a result of immunizations. Current data suggest that vaccination is an underused prevention strategy in the CKD and ESRD populations.[639] Potential barriers to immunization that are specific to the CKD populations have not been systematically examined. Although lower vaccine responsiveness has been widely recognized in the ESRD population, to what extent moderate to advanced CKD modifies vaccine responsiveness remains unclear.[640–642] Studies that have examined vaccination in the setting of CKD or ESRD have been limited by small study size, variable follow-up, and ascertainment of surrogates for vaccine effectiveness such as antibody response and rate of antibody decline after vaccination as opposed to vaccine efficacy for preventing infection.[643]

Influenza A and B vaccine. Despite potentially impaired antibody responses, a 2-year analysis of US Medicare claims data found that people vaccinated against influenza A and B on dialysis had a substantially lower chance of any-cause hospital admission and any-cause death than those patients not vaccinated on dialysis.[644] This finding might indicate clinical effectiveness of vaccinating this population but its observational design might also reflect differences in the underlying clinical status among people vaccinated and not

vaccinated. No unique adverse events related to influenza vaccine have been identified in people on dialysis.

Pneumococcal vaccine. People with kidney disease vaccinated with the pneumococcal vaccine seem to develop different serotype-specific titers, develop lower levels of antibody titers, and have a more rapid loss of antibody titers as compared with healthy control subjects.[639,645,646] Practitioners should be aware of the impact of specific vaccines on responsiveness and duration of responsiveness. Revaccination practices will be dictated by that knowledge.

Hepatitis B vaccine. Widespread hepatitis B virus (HBV) vaccination at the onset of dialysis has led to a marked reduction of HBV infections in people with ESRD, although improved screening of blood products and dissemination of recommendations for reducing the spread of HBV infections in dialysis units have also likely contributed.[647] Among people with moderate to advanced CKD, hepatitis B vaccination responsiveness has been shown to range from approximately 60 to 80% depending on the dosage, number of administered vaccines, and study population. Although findings have been inconsistent as to whether the level of GFR affects vaccine responsiveness in people with CKD[640,642] those with higher GFR are more likely to respond with seroconversion, independent of other factors.[640]

S. aureus vaccine. StaphVAX has not been shown to be efficacious in reducing the risk for Staphylococcus aureus bacteremia in people on hemodialysis.[648,649] No data are published in people with CKD.

Live vaccines. Due to the fact that people with CKD are often immunocompromised, live vaccines should only be used with caution on an individual basis.

In summary, although some vaccines (like influenza) in usual doses provide protection, other vaccines (HBV and pneumococcal) require more frequent dosing or larger doses to achieve and maintain protective antibody titers. Frequency and type of vaccination will vary according to local circumstances and prevalence of disease.

International Relevance

The availability of different vaccinations may vary worldwide, as does the prevalence of specific bacterial, viral, and other infections. It is reasonable to offer individuals appropriate immunization according to local practices.

Implications for Clinical Practice and Public Policy

Vaccines for influenza, hepatitis B, and pneumococcus are currently recommended for people with CKD by the local, regional, or national advisory committees on immunization practices from most countries.

Current recommendations are to:

- Provide influenza vaccination annually to people with CKD.
- Provide pneumococcal vaccine with a single booster dose 5 years after the initial dose.
- Provide HBV vaccine to people with CKD who are likely to require RRT. Although the recommendation is to give the HBV vaccine during more severe CKD (GFR <15 ml/min/1.73 m^2), it may be preferable to give this earlier to maximize the chances of achieving immunity; there are data to support this practice.[640] This would also ensure that all patients are immunized against HBV before receiving a transplant. As protective antibody levels may fall, this should be checked (possibly annually) with booster doses given if appropriate.

Areas of Controversy, Confusion, or Non-consensus

Much remains to be understood concerning impaired host response to infection in patients with CKD.

- Studies should be undertaken to determine the absolute rates, risk factors, and clinical course of different types of clinically relevant infections across the spectrum of CKD, by GFR and albuminuria category, and by cause.
- The outcomes across the range of acute infections in CKD population need to be ascertained.
- Studies should be undertaken to assess the rate of decline of antibody titers post-vaccination and the efficacy of immunization in people with CKD.

Pediatric Considerations

Current immunization schedules for children are regularly updated by both the US Centers for Disease Control and Prevention[650] and American Academy of Pediatrics.[651]

Current and comprehensive immunization recommendations for children with CKD have been published by Neu in 2012.[652] The paper addresses key issues regarding the use of vaccines in CKD pediatric populations who are receiving concomitant immunosuppression and in those awaiting transplantation. The need for, and interpretation of, protective antibody levels for those vaccines where this is indicated is described.

An oversimplified summary of the recommendations would be to provide all recommended childhood vaccines to every child with CKD with the exception of any live viral vaccine in a child receiving immunosuppressive medications. Likewise children on dialysis should not receive the live attenuated influenza vaccine although the inactivated version can and should be given to all children with CKD on an annual basis otherwise. Pneumococcal vaccination is particularly important in children with nephrotic syndrome and those with CKD, and current vaccination schedules and products should be carefully reviewed to ensure proper serotype coverage is being provided. Hepatitis B status and vaccination are of extreme importance in all children who may go onto dialysis – and specific recommendations for ongoing monitoring and interpretation of antibody levels should be carefully reviewed.

CKD and risk of AKI

Due to the epidemiological association between CKD and AKI and the number of observational studies reporting an association between pre-existing CKD and AKI, CKD is

considered the most consistent pre-existing condition associated with a high risk of AKI. However the potential linkage between patients with AKI, CKD, and ESRD has been inadequately studied to date and remains ill defined. This section describes AKI as a complication which needs to be managed in those with CKD. Given its association with progression, it is also described in that section.

4.6.7: We recommend that all people with CKD are considered to be at increased risk of AKI. (*1A*)

4.6.7.1: In people with CKD, the recommendations detailed in the KDIGO AKI Guideline should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. (*Not Graded*)

RATIONALE

Observational data suggest a strong association between pre-existing CKD and AKI. The appreciation that CKD patients may be more susceptible to AKI is the purpose of the above set of statements. However, methodological issues such as how CKD and AKI are defined in clinical studies and the statistical adjustments for non-uniformity of comorbidities among various studies may affect the validity of observed associations.

Evidence Base

CKD is designated as a risk factor for AKI because of the epidemiological association between the two.[263,264] A number of studies in a variety of settings report an association between pre-existing CKD and AKI. [265-271] CKD is a potent predictor of acute decline in kidney function following exposure to radiocontrast,[272] major surgery,[273] and other medical conditions.[274]

Hsu et al.[14] compared the pre-hospitalization MDRD GFR of 1764 adult members of the Kaiser Permanente Northern California health-care system who developed dialysis-requiring AKI during hospitalization with 600,820 individuals who did not. Compared with a reference baseline GFR of $\geq$60 ml/min/1.73 m^2, a baseline GFR of 45–59 ml/min/1.73 m^2 was associated with an adjusted OR of in-hospital AKI of 1.66 (95% CI 1.40–1.97). For GFR values of 15–29 ml/min/1.73 m^2, the adjusted OR for in-hospital AKI was 20.42 (95% CI 17.40–23.96). The presence of diabetes, hypertension, and proteinuria increased the likelihood of developing in-hospital AKI, with adjusted ORs of 1.99 (95% CI 1.78–2.23), 1.55 (95% CI 1.37–1.76) and 2.84 (95% CI 2.52–3.19), respectively. The authors concluded that CKD is the main risk factor for AKI during hospitalization. A contrasting approach by Singh et al. defined AKI as dialysis-requiring acute renal failure.[275] Because the clinical decision to dialyze a patient is frequently influenced by a higher overall SCr, presence of hemodialysis access, or consideration of inevitable progression to ESRD, this definition of AKI could bias toward capturing more AKI cases in CKD patients. Moreover, in patients with advanced CKD, the progression of CKD to ESRD may sometimes be difficult to separate from acute-on-chronic renal failure. A cohort study by Lafrance et al. followed a referred CKD population in British Columbia for a median of 19.4 months after achieving a GFR of $\leq$30 ml/min/1.73 m^2. Forty-five percent had at least one episode of AKI.[276] In another cohort study of 920,985 adults in Alberta, Canada with at least one outpatient measurement of SCr and proteinuria and not requiring chronic dialysis, risk of admission with AKI increased with heavier proteinuria and reduced GFR.[16]

International Relevance

These guidelines about AKI have relevance around the world. While the causes of AKI may differ by region, country, socio-economic status, and age, the consequences remain the similar. Where there are no facilitities to support AKI or CKD, people will die.

Areas of Controversy, Confusion, or Non-consensus

Interpretation of published data examining the influence of pre-existing CKD on the increased likelihood of AKI is potentially confounded by a number of issues. These include the comorbidities associated with CKD, influenced by repeated exposure to various nephrotoxic insults or in-hospital errors,[57,277] or primarily due to the altered physiology in CKD. There are also methodological issues such as how CKD and AKI are defined in clinical studies and the varying statistical adjustments for comorbidities which may affect the validity of observed associations.

A further important issue to clarify is whether pre-existing CKD influences the outcome of AKI. Currently, there is no single biomarker that can differentiate 'acute' from 'chronic' kidney disease and help to address this issue. Several large observational and database studies report, surprisingly, lower in-hospital mortality in patients with AKI superimposed on CKD compared with controls.[278-283] Data from PICARD reveal lower in-patient mortality and median length of stay in ICU subjects with acute-on-chronic renal injury compared with non-CKD subjects with AKI, though the post-discharge dialysis rates were higher in subjects with pre-existing CKD.[284]

Pediatric Considerations

The relative paucity of pediatric specific guidelines (due to lack of high-quality studies) in the KDIGO AKI guideline would suggest that the use of pediatric data and review papers as well as relevant pediatric nephrology texts would be of benefit to the practitioner interested in reviewing this topic in greater detail and applying pediatric data to their practice.[653–658]

RESEARCH RECOMMENDATIONS

Prospectively designed clinical studies with a clear and uniform definition of CKD and AKI and adjusted for comorbidities are needed to determine:

- the frequency of AKI events in a CKD population
- the outcome of AKI in patients with CKD condition

- the importance of proteinuria in addition to low GFR in the risk of AKI

CKD and risk of hospitalization and mortality

Regardless of the method used to estimate GFR, hospitalization and mortality rates are higher in people with CKD. Exact rates vary with comorbidity and severity of CKD, and are not well-defined. Selection of interventions that could reduce hospitalizations, morbidity, mortality, and costs in people with CKD is not well-studied.

4.6.8: CKD disease management programs should be developed in order to optimize the community management of people with CKD and reduce the risk of hospital admission. (*Not Graded*)

4.6.9: Interventions to reduce hospitalization and mortality for people with CKD should pay close attention to the management of associated comorbid conditions and cardiovascular disease in particular. (*Not Graded*)

RATIONALE

There are observational and database studies reporting an association between pre-existing CKD and hospitalizations and mortality. A better understanding of the rates, causes, and risk factors for hospitalization among people with CKD would allow estimates of the economic burden of CKD and identification of those at risk for increased resource utilization. People with CKD are an ideal target for interventions aimed at reduction of morbidity, hospitalization, mortality, and costs. These statements suggest that a coordinated approach to the identification and management would result in better outcomes and are intended as 'best practices' statements, recognizing the difficulty in developing an evidence base while addressing issues related to resource allocations (Table 34).

Evidence Base

Mortality rates remain high (16-22%) with the use of dialysis, with more than half of all deaths related to CVD. Less is known about mortality and CVD rates, and resource use among persons with a reduced GFR who are not yet receiving maintenance dialysis. Few studies have investigated the association between CKD and the risk of hospitalization.

Data from the USRDS reveal that hospitalization rates vary with comorbidity and interact with degrees of CKD. Adjusted rates are 38% higher in people with CKD and 19% greater in people with CKD and GFR under 60 ml/min/1.73 m^2 than in those with GFR >60 ml/min/1.73 m^2, who in turn are 20% higher than in people without CKD-illustrating the graded impact of advancing kidney disease. Not surprisingly, rates of cardiovascular hospitalization are greater for people with CKD, particularly those with increasing severity of CKD.[659] In both the CKD and non-CKD populations, adjusted rates of hospitalization increase with greater comorbidity. In 2008, for example, the rate for people with CKD with both diabetes and CHF was 726 per 1000 person-years at risk — 85% greater than the rate of 393 among people with neither diagnosis. Rates of admission for CVD increase even more in the higher categories of GFR. Among Medicare subjects, the rate of 141 admissions per 1000 person-years for those with GFR <60 ml/min/1.73 m^2 is 26% higher than the rate of 112 reported for those with CKD and GFR ≥ 60 ml/min/1.73 m^2. The admission rates of 101 and 90 reported for MarketScan and Ingenix i3 subjects with GFR <60 ml/min/1.73 m^2 are 48 and 16% greater, respectively, than those occurring in people with higher GFRs.[633] Adjusted rates of mortality in USRDS 2008 increased with age, and were highest in people with advanced categories of GFR: 31–72% higher, for example, in people with GFR <60 ml/min/1.73 m^2 compared to those with no CKD. By gender, rates in men with CKD were 91.8 per 1000 person-years at risk compared to 85.6 in women. Rates for people with CKD overall were similar in whites and African Americans, but in people with GFR <60 ml/min/1.73 m^2, rates for African Americans were 18% higher than those for whites, at 95.0 and 80.5 per 1000 person-years, respectively.[633]

Khan et al.[660] confirmed that hospital utilization among people with CKD is high. During a median follow-up of 11.4 months, 47% of subjects had at least one hospitalization and there were on average 0.96 hospitalizations, 6.6 hospital days, and 4.0 outpatient nephrology visits per person-year at risk. Cardiac disease/hypertension was the most common primary diagnosis of hospitalizations and progression of CKD/acute kidney failure was the most common secondary cause of hospitalization. The authors had previously shown that the dialysis population at their institution had 2.2 hospitalizations and 14.8 hospital days per person-year at risk,[659] which was similar to that among US hemodialysis patients between 1996 and 1998, who had 1.9 hospitalizations and 14 hospital days per person-year at risk.[661] In the general population, there were 0.31 hospitalizations and 1.9 hospital days per person in 1998.[662]

Go et al.[58] reported an independent, graded association between GFR and the risk of death, cardiovascular events, and hospitalization in 1,120,295 adults within a large, integrated system of health-care delivery in whom SCr had been measured between 1996 and 2000 and who had not

Table 34 | Components of community CKD management programs

Disease monitoring
Integration with other chronic disease management programs including diabetes, hypertension and heart failure
Medication management and dietary advice
Anemia management programs
Vaccination programs
Information and psychosocial support
Renal replacement therapy (dialysis and transplant) education
Advanced care planning and end-of-life care (where appropriate)

Abbreviation: CKD, chronic kidney disease.

undergone dialysis or kidney transplantation. These risks were evident at GFR <60 ml/min/1.73 m^2 and substantially increased at GFR <45 ml/min/1.73 m^2.

The higher hospital utilization among people with CKD compared to the general population, and the similarity in the comorbid conditions and the causes of hospitalization between people with CKD and ESRD, confirm the hypothesis that the complications and comorbidity observed in ESRD are manifest earlier in the disease process. Previous studies have demonstrated an association between age, gender, race, cardiac disease, peripheral vascular disease, serum albumin and hematocrit levels, and resource utilization among people on dialysis.[659,663,664] Holland et al.[665] identified baseline predictors of first non-elective hospitalization among a retrospective cohort of 362 predialysis subjects. Multivariate analysis, adjusted for baseline creatinine concentration, selected advanced age (RR 1.02; 95% CI 1.01–1.03), angina (RR 1.9; CI 1.37–2.61), peripheral vascular disease (RR 1.55, CI 1.05–2.27), and Hb concentration (RR 0.99, CI 0.94–0.98) as independent predictors of hospitalization. These comorbid conditions progressively worsen with advancing kidney disease and result in a substantial proportion of people having severe complications by the time they come to RRT.

Interventions to reduce hospitalizations and mortality for people with CKD should pay close attention to the management of associated comorbid conditions and CVD.[666] Closer attention to the management of heart disease in this population could substantially improve outcomes.[667]

The influence of correction of anemia on hospitalization is controversial. Drüeke et al.[668] randomly assigned 603 subjects with GFR 15-35 ml/min/1.73 m^2 and mild-to-moderate anemia (Hb level: 11.0-12.5 g/dl [110-125 g/l]) to a target Hb value in the normal range (13.0-15.0 g/dl [130-150 g/l]) or the subnormal range (10.5-11.5 g/dl [105-115 g/l]). There were no significant differences between the two groups in the incidence of hospital admission (61% and 59%, respectively) or mean duration of hospitalization for cardiovascular reasons (33.0 and 28.2 days, respectively). Singh et al.[669] studied 1432 people with CKD, 715 of whom were randomly assigned to receive a dose of epoetin alfa targeted to achieve a Hb level of 13.5 g/dl (135 g/l) and 717 of whom were assigned to receive a dose targeted to achieve a level of 11.3 g/dl (113 g/l). The median study duration was 16 months. The primary end point was a composite of death, MI, hospitalization for CHF (without RRT), and stroke. They observed an increased risk of the primary composite end point in the high Hb group as compared with the low Hb group. Death and hospitalization for CHF accounted for 74.8% of the composite events. The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)[375] study involved 4038 people with diabetes, CKD, and anemia. Subjects were randomly assigned to treatment with darbepoetin alfa to achieve a Hb level of approximately 13 g/dl (130 g/l) or to placebo, with rescue darbepoetin alfa when the Hb level was less than 9.0 g/dl (90 g/l). The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal MI, CHF, stroke, or hospitalization for myocardial ischemia) and of death or ESRD. Again there were no significant between-group differences in the outcomes of interest.

International Relevance

It is of benefit for all jurisdictions to appreciate the increase in resource utilization by CKD populations. Identification of people at risk for increased resource utilization and economic burden of CKD should result in strategies to attenuate that risk or address the resource implications. Selection of interventions that could reduce hospitalizations, morbidity, mortality, and costs in these populations should be evaluated.

DISCLAIMER