Management of Cardiovascular Disease in Chronic Kidney Disease: Implications for Managed Care

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Abstract

Despite the rising incidence of chronic kidney disease (CKD), this condition remains underrecognized and is costly to treat. Care of CKD accounts for a substantial portion of US Medicare spending, with major costs primarily associated with hospitalization and drug therapy. The leading cause of death and hospitalization in patients with CKD is cardiovascular disease (CVD). Strategies to improve identification of CKD have proved to be cost-effective in the highest risk patients (eg, those with diabetes), but determining the most appropriate way to identify high-risk patients remains a significant challenge. There is also evidence to suggest that referral to a specialist once the estimated glomerular filtration rate reaches approximately 60 mL/min/1.73 m^2 is cost-effective, especially when patients are greater than 50 years of age and/or have diabetes. Individualized patient care has shown to be cost-effective (or even cost saving), and associated with improved outcomes, such as reduced incidence of CVD events and mortality. Individualized care centers treat numerous comorbidities (eg, hypertension, diabetes, albuminuria, dyslipidemia) in a given patient to prevent the downstream consequences of worsening CVD. Ensuring access to specialist care and effective therapies, along with adherence to such therapies, appears to be a cost-effective, or even cost-saving, strategy based on current available evidence.

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For author information and disclosures, see end of text.

An increasing public health concern, chronic kidney disease (CKD) is rising in incidence, from 10% of the US population between 1988 and 1994 to 13% 10 years later.[1-3] CKD is associated with substantial morbidity and mortality. The leading cause of death in patients with CKD is cardiovascular disease (CVD), accounting for approximately 100 deaths per 1000 patient-years.[1,4] CVD occurs as a direct effect of CKD and the contribution of commonly experienced CVD risk factors, such as diabetes, hypertension, dyslipidemia, and proteinuria. The contribution of numerous underlying comorbid conditions and high rates of hospitalization and CVD events (eg, stroke, myocardial infarction [MI], heart failure, hospitalization) result in a tremendous economic impact to the patient with CKD and the healthcare system.[5] In one study, patients with CKD had 65% higher 10-year healthcare costs than non-CKD patients.[5] Inpatient treatment and drug costs, but not outpatient costs, primarily accounted for these differences. Angina, MI, diabetes, and anemia also strongly influenced costs.[5]

From a managed care perspective, the CKD population must be accurately identified. Patients should be assessed for needed treatment, and treatment should be delivered in an evidence-based, cost-effective way. Use of inappropriate or ineffective therapies should be minimized or eliminated when possible.[6] Correct identification and early treatment of CKD is important because it is a progressive disease. Evidence from predictive modeling studies suggests that 11% of patients with a creatinine clearance less than 60 mL/min (stage 3 CKD) will eventually reach a creatinine clearance less than 15 mL/min (stage 5), and overall, 3.7% of patients will develop end-stage renal disease (ESRD) requiring dialysis or transplantation.[7] This article will evaluate the importance of appropriately identifying patients with CKD and managing CVD risk to enhance quality and cost-efficiency of care in the CKD population.

Costs Associated With CKD

Although patients with CKD comprise 6.8% of the US Medicare population, these individuals consume over 14% of overall Medicare expenditures.[1] The overall Medicare cost per person per year for CKD was $19,752 in 2008. Costs in the subset

of Caucasian patients with CKD and diabetes were $21,740, $25,352 for African American patients with CKD and diabetes, and $28,809 and $35,009 in respective heart failure cohorts with CKD.[1] A review article examining costs of glomerular filtration rate (GFR) monitoring determined the annual medical costs in patients with and without CKD 65 years and older. In that paper, the average annual costs were $20,784 for all patients with CKD, $11,760 for patients with a creatinine clearance greater than 60 mL/min, and $68,808 for those with ESRD, indicating that the costs increase as kidney disease progresses.[8] The review also determined that death was an important cost to consider in patients with CKD, and estimated the onetime cost of death at $37,611.[8]

Chronic conditions (eg, obesity, hypertension, MI, angina, diabetes, dyslipidemia, anemia, and hyperuricemia) are also associated with an increase in cost of care in patients with CKD.[5] The leading reason for hospitalization in patients with CKD is CVD.[1] In addition to chronic costs associated with CKD and incident CVD, costs of dialysis initiation and maintenance are also major cost factors.[9] To address the issue of the importance of comprehensive care in patients with CKD at risk for requiring dialysis, one study randomized 69 patients to nephrologist care and 71 patients to a CKD care program which included a nephrologist, trained nurses, and a dietitian with specific goals for patient education.[9] The comprehensive program to improve pre-ESRD care was associated with lower total medical costs at dialysis initiation ($942 vs $2674; P <.001) due to early preparation for vascular access and avoidance of hospitalization at dialysis initiation.[9] Providing specialized comprehensive care to patients with CKD is important because, in the US healthcare system, inappropriate care leads to unnecessary costs. A recent review noted that in managed care populations, unneeded or inappropriate care is delivered as much as 30% of the time, resulting in unnecessary costs. If resources were added to improve the frequency of appropriate care to more than the current value of approximately 50%, it would be possible to improve outcomes and reduce overall costs.[6] Recognizing that care of the CKD population is often inappropriate, and that the costs of managing CKD are high, early identification and specialized management of CKD is likely to significantly reduce cost of care to the patient and the healthcare system.

Identification of Patients With CKD

As mentioned in the first article in this supplement,[10] elevated serum creatinine is an indicator of reduced kidney function, but it is not a sensitive measure. GFR, a more accurate reflection of kidney function, is dependent on other factors (eg, sex, body weight/body mass, and ethnic background). Unfortunately, it is impractical to routinely measure GFR because of the complexity, expense, and time involved, so clinicians routinely estimate GFR in order to stage CKD and make treatment decisions. The Modification of Diet in Renal Disease and the CKD-Epi equations are most commonly used to estimate GFR by incorporating serum creatinine, age, sex, and race.[1,3,11] Recent data have suggested that addition of other factors (eg, cystatin C, urinary albumin-to-creatinine ratio) improves estimation of kidney function and the consequent CVD risk.[12,13] The value of these tests in practice remains to be determined, especially in settings where the incidence of CKD is unappreciated. Current clinical practice guidelines recommend recognition of CKD and appropriate treatment as early as possible, but there are a number of barriers.[1] The remainder of this section will address attempts to improve recognition of CKD, and later sections will review the delivery of appropriate treatment.

One current barrier to appropriate CKD care is that CKD is underrecognized by primary care physicians and specialists.[14] In one recent study of managed care patients with an estimated GFR of 10 to 60 mL/min/1.73 m^2, only 14.4% had a documented CKD diagnosis.[14] In a multivariate analysis, physicians were more likely to document CKD among patients of older age and lower estimated GFR (P <.001 for each 10 mL/min incremental decline below 50 mL/min), but the presence of CVD, cerebrovascular disease, peripheral arterial disease, and heart failure did not improve recognition of CKD. CKD was also documented to a lower degree in women compared with men.[14]

One intervention to improve CKD recognition was the implementation of mandatory reporting in certain states. In 2007, laboratories in Connecticut, Louisiana, Michigan, New Jersey, Pennsylvania, and Tennessee were mandated to automatically provide estimated GFR when a serum creatinine test was requested. In a study examining the cost and benefit of this approach, reporting estimated GFR was associated with a cost-effectiveness ratio (CER) of $16,751 per quality-adjusted life-year (QALY), while reporting serum creatinine alone had a CER of $16,779 per QALY.[8] Simulations for a hypothetical cohort of 10,000 patients over 10 years estimated 13 fewer deaths, 29 fewer ESRD events, and 11,348 more false positive CKD cases. The potential cost benefit of automatic estimated GFR was negated by the impact of a false positive test on QALYs.[8] Because a spuriously low GFR could lead to unnecessary tests and treatments, and associated decline in QALYs, this practice of automatic reporting must be carefully considered by clinicians and policy makers with regard to how the test is interpreted. It is likely that

action should be taken based on a trend over time, rather than based on an isolated value.

Another way to evaluate patients for CKD is to target screening in at-risk populations. A study determined the impact of population-based screening for CKD, as compared with screening of patients with diabetes or hypertension. The cost per QALY (2009 Canadian dollars) for population screening (vs no screening) was $104,900, with an expected decline in the number of patients developing ESRD from 675 to 657 per 100,000 patients. By comparison, the cost per QALY was $22,600 for diabetics and $572,000 for nondiabetics, $334,000 for patients with hypertension, and $411,100 for those without hypertension.[15] These results suggest that screening of patients with diabetes for CKD is a cost-effective intervention.

Another study that evaluated annual microalbuminuria screening (beginning at 50 years of age) found a CER per QALY of $73,000 relative to nonscreening, and $145,000 relative to usual care. Usual care was defined as annual screening for 22% of diabetics, 2% of hypertensives, and 23% of patients with diabetes and hypertension. Relative to no screening, the CERs per QALY were $21,000 for diabetics, $55,000 for hypertension, and $155,000 for patients without diabetes or hypertension.[16] These results indicate that strategies to improve identification of patients with CKD may be cost-effective (<$50,000 CERs per QALY), particularly in patients with diabetes.

When patients with CKD have been identified, care may be improved by referral to a specialist. The goal of identification of patients with CKD is to deliver the most appropriate treatment to prevent or treat comorbid conditions (eg, CVD) and to slow the progression of kidney disease. A systematic review summarized the cost-effectiveness (2006-2007 pounds) of early referral strategies to a nephrologist to provide better kidney and cardiovascular care.[17] In that review, the incremental CER per QALY relative to standard care ranged from £4091 (approximately $6750) for referral at CKD stage 3a to £5923 (approximately $9770) for referral at stage 4.[17] A large part of the improvement in QALYs was attributed to improvements in CVD care. Based upon these findings, authors of the study recommended referral to a nephrology specialist as warranted under several circumstances including: (1) patients with stage 4 or 5 CKD; (2) when the albumin-creatinine ratio (ACR) is at least 70 mg/mmol and not due to diabetes; (3) when ACR is 30 mg/mmol with hematuria and rapidly declining GFR is observed; (4) poorly controlled hypertension despite 4 antihypertensive drugs; (5) suspected genetic cause of CKD; and (6) renal artery stenosis.[17] It is also recommended that patients with renal outflow obstruction be seen by a urologist.[17]

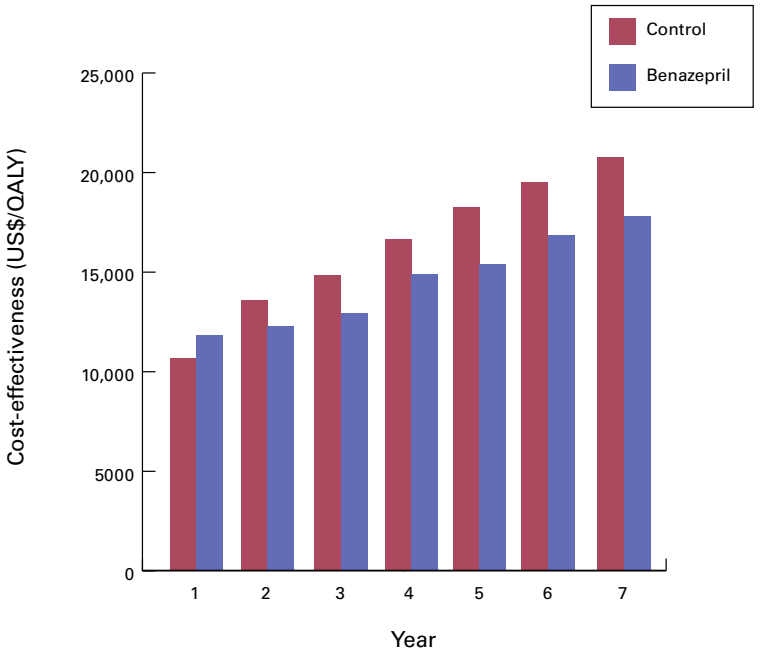
Treatment of CVD in CKD

Articles on the managed care perspective of a disease often focus on prevention rather than treatment. In the case of CKD, many of the comorbid conditions are already present at baseline and remain prevalent throughout the disease.[10] The goal of therapy is to limit the risk of hospitalization for acute events and delay disease progression. Recognition of CKD and assessment of CVD risk factors is critical to the prevention of ESRD, and delivery of the most appropriate treatments. In a previously mentioned managed care study,[14] subjects documented by their caregiver to have CKD compared with those without documented CKD were more likely to receive appropriate care; 61% were more likely to use an angiotensin-converting enzyme inhibitor (ACEI) (P <.0001), 67% were more likely to use an angiotensin receptor blocker (ARB) (P = .008), 27% were more likely to use an HMG-CoA reductase inhibitor (statin) (P = .0014), and 37% were less likely to use a nonsteroidal anti-inflammatory drug (P <.0001). This indicates that the first step in delivery of appropriate management of CKD is the identification of the presence of CKD.

Recent evidence highlights that management of multiple risk factors may simultaneously increase quality of care and reduce cost of care. For example, random care for blood pressure (BP) will increase costs to prevent MI and stroke. Isolated treatment of BP according to Joint National Committee hypertension guidelines without regard to other risk factors may also lead to slightly higher costs to prevent MI and stroke. However, treating multiple CVD risk factors using patient-individualized guidelines can decrease overall costs with improved outcomes.[18,19] These facts suggest that a comprehensive approach to the patient, rather than isolating treatment to a specific indication, or focusing on a single guideline, can be a more economically feasible approach to care. It is interesting to speculate that this concept may be applied directly to patients with CKD, but since study populations had very low risk of CKD, any related assumptions could not be determined.[18,19] It stands to reason, however, that holistic evaluation and treatment of the patient and all associated problems will improve care, especially when treatment modalities can be used to treat multiple targets. Unfortunately, there are few formal cost-effectiveness studies of interventions to improve CVD outcomes in patients with CKD.

Despite a lack of formal intervention studies prospectively designed to evaluate the outcomes associated with treatment of CVD risk factors in patients with CKD, much has been learned from studying the relationship between treatment and outcomes based on CKD markers, such as GFR and albu-

Figure 1. Cost-Effectiveness (cost divided by quality-adjusted life-years in 1999 US dollars) of Benazepril Versus Control for 7 Years in Management of Hypertension in CKD[23]



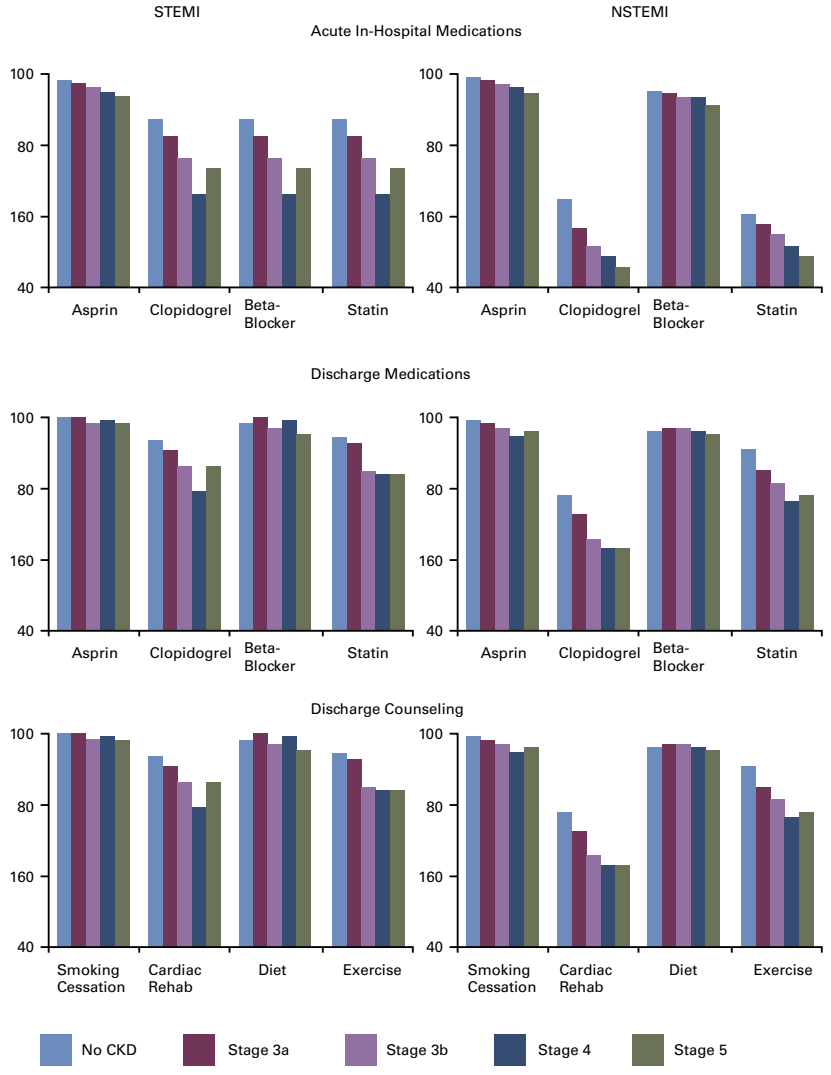
CKD indicates chronic kidney disease; QALY, quality-adjusted life-year.

minuria. In hypertension associated with CKD, treatment of albuminuria should be considered an integral part of care. In one study lasting approximately 5 years in 8206 patients with left ventricular hypertrophy, use of the ARB losartan to lower BP and albuminuria reduced the composite end point of cardiovascular mortality, stroke, and MI (independent of BP reduction).[20] Evidence suggests that the goal BP in patients with CKD should be less than 130/80 mm Hg unless proteinuria exceeds 1g/L, in which case it should be less than 125/75 mm Hg.[21] In another study which sought to determine the effect of trandolopril on survival where BP reduction was studied in the absence of documented albuminuria, the ACEI trandolopril did not improve survival in the overall cohort with relatively normal GFR.[22] In a subgroup analysis of patients with GFRs less than 60 mL/min/1.73 m^2, reduction of BP with trandolopril decreased cardiovascular and all-cause mortality (P = .02).[22] Finally, in a formal, 7-year economic analysis conducted on the ACEI benazepril for blood pressure control,[23] the CER per QALY demonstrated reduced cost ($10,000-$13,000) over the course of the study, due to improvements in outcomes (**Figure 1**). These results suggest that ACEI therapy in CKD (GFR <60 mL/min/1.73 m^2) may improve cardiovascular outcomes and result in cost savings.[23]

It should be noted, however, that despite nearly universal awareness of hypertension, adequate control of BP in accordance with current consensus standards remains highly suboptimal.[24] A recent study was conducted to determine community-based factors associated with awareness of hypertension, treatment patterns, and control rates using multivariable statistical adjustment. The study evaluated factors associated with BP control and lack of BP control in patients with a GFR of 20 to 70 mL/min/1.73 m^2, and found that ACEIs and ARBs were associated with enhanced BP control. Older patients, African Americans, and those with higher urinary albumin excretion were less likely to achieve BP control after multivariable adjustment.[24] In light of these findings, it is interesting to speculate that the lack of BP control in patients with CKD, or lack of ACEI and ARB therapy, may potentially be due to concerns among clinicians that ARBs and ACEIs are associated with GFR reductions and the risk of acute kidney injury.[25] Because of the documented benefits of ACEIs and ARBs in hypertension, diabetic nephropathy, heart failure, and coronary artery disease (CAD), these agents should be used with caution rather than avoided in patients with CKD.

The impact of ACEIs and ARBs on reduction of GFR is also commonly considered a therapeutic tool for management of proteinuria associated with diabetes. ACEIs and ARBs are the most well-studied agents for prevention of progression of CKD in diabetes, and they have also been studied extensively for their effects in CVD.[25-27] In 2 large diabetic nephropathy studies, despite slowing progression to ESRD, losartan and irbesartan failed to improve cardiovascular outcomes or death, suggesting a potential inadequate follow-up period to assess effects (or lack of effects) on CVD.[26,27] Clearly, patients with CKD and diabetes should be managed with a patient-specific, customized approach (rather than given a specific agent) due to the frequent presence of concomitant hyperglycemia, dyslipidemia, and hypertension.[28] In an economic evaluation examining the cost-effectiveness of a multifactorial approach to reducing CVD in diabetes, patients were randomized to the Diabetes Care Protocol (DCP) or usual care.[29] The DCP consisted of a 1-hour consultation by a practice nurse and computerized decision support software assessment that provided patient-specific advice (on targets for glycosylated hemoglobin, blood pressure, body weight, cholesterol, and smoking) and feedback to the

Figure 2. In-Hospital Medications, Discharge Medications, and Discharge Counseling in Patients with MI According to CKD Stage[33]



CKD indicates chronic kidney disease; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; STEMI, ST-segment elevation MI. Crude rates of acute in-hospital medications (within 24 hours), discharge medications, and discharge counseling by CKD status. All *P* values test for trend across CKD stage <.001 except for aspirin as a discharge medication and referral to cardiac rehabilitation (STEMI; *P* [trend] = .02 for both), and beta blockers as a discharge medication (*P* [trend] = .50 [STEMI], *P* [trend] = .12 [NSTEMI]). The "no CKD" category is limited by lack of information on albuminuria.

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practice and patient every 3 months. The incremental CER was €38,243 ($55,307) per QALY in the overall population. In patients with CVD, the CER was €14,814 ($21,424) per QALY, and the CVD costs were reduced by €587 ($849) (*P* <.05). In contrast, the CER per QALY for diabetic patients without CVD was €121,285 ($175,402). It should be noted that this study did not specifically address patients with CKD, but did demonstrate that diabetic patients with CVD could be treated in a cost-effective, and potentially cost-saving, manner using a comprehensive intervention.[29]

A Cochrane review evaluated the effects of statins in patients with CKD who did not require dialysis.[30] The evaluation consisted of 25,017 patients from 26 studies, and demonstrated a statin-induced reduction in low-density lipoprotein cholesterol (-42.38 mg/dL), total cholesterol (-41.48 mg/dL), all-cause death (19% reduction), cardiovascular death (20% reduction), and 24-hour urinary protein excretion (-0.73 g/24 hours). Statins appeared to be well tolerated, with associated adverse effects similar to those in controls.[30] The therapeutic benefits observed in the Cochrane review are consistent with recent trials.[31] In the absence of well-designed cost-effectiveness studies, it may be inferred that statins, with their established benefits and tolerability, appear to be a worthwhile intervention for patients with CKD and dyslipidemia or CVD.

To a similar extent, evidence on the cost-effectiveness of interventions for CAD, MI, and heart failure in patients with CKD is lacking.[32-34] However, similar trends are noted—standard therapies are effective, but they are underutilized.[33] As a case example (shown in **Figure 2**), standard therapies for MI (eg, ACEIs, ARBs, beta-blockers, aspirin, statins) are underutilized in patients with CKD, despite current evidence supporting their use in the presence of CAD or heart failure.[32-34]

Efforts to improve adherence are another important consideration in the treatment of CVD in CKD. In a 2007 survey of patients with Medicare Part D prescription drug plans, 23% to 31% of patients with ESRD reported cost-related nonadherence to prescription medication in the preceding 6 months, and patients with ESRD (vs those without ESRD) were 2.34-fold more likely to report cost-related nonadherence.[35] African Americans and patients with Medicare Part D Low-Income Subsidy assistance had higher rates of cost-related nonadherence in the multivariate analysis.[35] Any treatment decisions should include an assessment of

the patient's ability to pay, as well as the availability of well-tested, less costly generic options, especially when the regimen may be complicated and involve multiple medications.

In another study evaluating a privately insured population, patients taking medication for hypertension, dyslipidemia, and/or diabetes between 2004 and 2008 were evaluated for adherence (days per year covered by filled prescription).[36] In that study, adherence (defined as a medication possession ratio of 80% or more) was highest with medications for diabetes, followed by agents for hypertension and dyslipidemia. Interestingly, adherence was highest among patients taking the most medications (ie, those treated for all 3 conditions).[36] Enhanced compliance when multiple conditions are treated supports the theory that recognition of disease improves delivery of treatment. This is especially important for patients with CKD because they tend to have multiple comorbidities and consequently require numerous medications. The suggestion that taking more medications results in better compliance is encouraging, because it may mean that if patients with CKD can be identified, they can be partners in their care with more adequately followed therapeutic regimens.

Summary

In patients with CKD, the key factor associated with delivering the most effective therapy is correctly identifying patients. However, in practice, identification of patients with CKD has proved to be a challenge for clinicians. Strategies to improve identification of CKD, such as mandatory GFR reporting and promotion of annual screening, are increasing awareness and have proved to be cost-effective in at least a subset of those at greatest risk for complications (eg, those with diabetes). Based on limited formal economic analyses in the CKD population, it appears that interventions which target CVD risk factors, such as hypertension, albuminuria, dyslipidemia, and diabetes, are effective in lowering CVD events and mortality. These therapies may be cost-effective or even cost saving, due primarily to the high costs associated with CVD hospitalization and death, and the cost savings associated with avoiding these events. Additional considerations to improve care include ensuring appropriate access to affordable medications, and eliminating inappropriate or ineffective therapies which may negatively impact therapeutic outcomes and lead to higher overall healthcare costs.

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