

## CLINICAL GUIDELINES

## Guidelines for the management of chronic kidney disease

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∞ See related commentary by Eknoyan, page 1107

New guidelines for the management of chronic kidney disease have been developed by the Canadian Society of Nephrology (Appendix 1 contains the full-text guidelines; available at [www.cmaj.ca/cgi/content/full/179/11/1154/DC1](http://www.cmaj.ca/cgi/content/full/179/11/1154/DC1)). These guidelines describe key aspects of the management of chronic kidney disease to facilitate shared care for these patients by general practitioners and specialists, including internists, endocrinologists, cardiologists and nephrologists. Specifically, these guidelines are for the care of patients who are not receiving dialysis. In this review, we outline recommendations from the guidelines on aspects of management of chronic kidney disease, including targets for various abnormalities, strategies for treatment and the frequency of follow-up based on the evidence available.

Chronic kidney disease is estimated to affect between 1.9 million and 2.3 million Canadians. It constitutes a major public health problem.<sup>1</sup> Chronic kidney disease often coexists with cardiovascular disease and diabetes and is recognized as a risk factor for all-cause mortality and cardiovascular disease.<sup>2-4</sup>

The definition of chronic kidney disease has been simplified over the last 5 years. It is now defined as the presence of kidney damage for a period greater than 3 months. An estimated or measured glomerular filtration rate of less than 60 mL/min/1.73 m<sup>2</sup> is considered abnormal for all adults. A rate of more than 60 mL/min/1.73 m<sup>2</sup> is considered abnormal if it is accompanied by abnormalities of urine sediment or abnormal results of imaging tests, or if the patient has had a kidney biopsy with documented abnormalities.<sup>5</sup> As the reporting of estimated glomerular filtration rates has become more common, the relatively high prevalence of impaired kidney function (i.e., estimated glomerular filtration rate < 60 mL/min/1.73 m<sup>2</sup>) has become evident.<sup>6</sup>

The National Kidney Foundation in the United States has published a classification system based on glomerular filtration rate as well as urinary and anatomic abnormalities (Table 1) to enhance the identification and management of chronic kidney disease.<sup>5</sup> Controversies exist in the literature as to the validity of this classification system based on esti-

## Key points

- Chronic kidney disease is common and is associated with increased cardiovascular risk.
- Attention to cardiovascular risk factors remains the cornerstone of care to delay progression of chronic kidney disease and prevent cardiovascular events.
- Randomized clinical trials are lacking; thus, recommendations in the guidelines are based on a synthesis of the best available evidence.
- Shared care of patients with chronic kidney disease by general practitioners and specialists is encouraged.

mated glomerular filtration rate for certain patient groups. However, awareness and attention to chronic kidney disease have increased since the publication of this staging system and the surrounding education.<sup>7</sup>

Most patients with chronic kidney disease will die of events related to cardiovascular disease before end-stage renal disease develops.<sup>8</sup> Therefore, an important focus of care for patients with chronic kidney disease includes management of cardiovascular risk factors. These guidelines are the first integrated publication to guide and optimize care for patients with chronic kidney disease. As part of a national strategy that incorporates chronic disease management, these guidelines serve as a starting point for ensuring optimal management of care for these patients. Guidelines, however, do not replace clinical judgment or the need for a nephrology consultation if questions arise.

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Clinical practice guidelines for the management of chronic kidney disease that does not require dialysis have been developed in the United Kingdom, Australia and the United States. The Canadian guidelines are unique because they include an in-depth evaluation of a broad range of topics in the management of chronic kidney disease, are based on the most recent evidence and are aimed at front-line physicians (both general practitioners and specialists).

## Development of the guidelines

We initially divided the management of chronic kidney disease into key topic areas. We assigned each topic to nephrologists and content experts within the field (Appendix 2, available at [www.cmaj.ca/cgi/content/full/179/11/1154/DC1](http://www.cmaj.ca/cgi/content/full/179/11/1154/DC1)) who performed a systematic review of the literature from which relevant recommendations were developed. The topics were chosen based on their importance in the management of chronic kidney disease, as well as the existence of an evidence base. In addition, we have included topics that do not have a substantial direct or indirect evidence base but are important for practitioners and patients (e.g., preparation for care of end-stage renal disease and comprehensive conservative management).

Each recommendation was graded using the scheme developed by the Canadian Hypertension Education Program<sup>9</sup> and used by the Canadian Society of Nephrology Guidelines Committee (Appendix 3, Appendix 4, available at [www.cmaj.ca/cgi/content/full/179/11/1154/DC1](http://www.cmaj.ca/cgi/content/full/179/11/1154/DC1)).<sup>10</sup> The criteria for grading these recommendations range from those reflecting highly valid, precise and applicable studies (grade A) to those based on lower level evidence and expert opinion (grade D). Grades B and C refer to studies of lesser degrees of validity, including surrogate outcomes or extrapolation of study results to other populations. The final draft of the guidelines was reviewed by experts and external stakeholders, including other relevant associations, to ensure consistency with other guidelines.

We developed the clinical practice guidelines statements using best evidence where available. In cases where evidence did not exist, we provide the clinical practice recommendations along with the rationale. The full text of each discrete subject area is available online (Appendix 1, available at [www.cmaj.ca/cgi/content/full/179/11/1154/DC1](http://www.cmaj.ca/cgi/content/full/179/11/1154/DC1)) and in-

cludes the rationale for the statements, the evidence base and the relevant background. A summary of the guidelines is provided in Appendix 5 (available at [www.cmaj.ca/cgi/content/full/179/11/1154/DC1](http://www.cmaj.ca/cgi/content/full/179/11/1154/DC1)).

It is important to recognize that the major risk for patients with chronic kidney disease is death from cardiovascular disease or diabetic complications. As a consequence, we chose to align the guidelines with those from the Canadian Diabetes Association, the Canadian Hypertension Education Program, and the Canadian Cardiovascular Society.

## Clinical recommendations

### Referral of adult patients with reduced kidney function

Guidance for primary care providers and specialists for the referral of patients with chronic kidney disease to nephrologists are available ([www.csnsn.ca](http://www.csnsn.ca)). Most cases of nonprogressive chronic kidney disease can be managed without referral to a nephrologist. Referral to a nephrologist is generally recommended for patients with acute kidney failure, persistent estimated glomerular filtration rate less than 30 mL/min/1.73 m<sup>2</sup>, progressive decline of kidney function, ratio of urine protein to creatinine greater than 100 mg/mmol (about 900 mg/24 h) or urine albumin to creatinine ratio greater than 60 mg/mmol (about 500 mg/24 h), inability to achieve treatment targets, or rapid changes in kidney function.

### Hypertension

Hypertension is commonly associated with chronic kidney disease. It develops in more than 75% of patients with chronic kidney disease at any stage.<sup>10</sup> It is both a cause and a consequence of chronic kidney disease. This section of the guidelines highlights key aspects of the management of hypertension in patients with chronic kidney disease. These aspects include target blood pressure, initial drug therapy for proteinuric and nonproteinuric chronic kidney disease, and treatment of hypertension in association with diabetes and large-vessel renal vascular disease (Box 1).

### Diabetes

Patients with diabetes are at increased risk for chronic kidney disease and cardiovascular events. The control of blood glucose levels in patients with chronic kidney disease may be problematic because of increased or changing sensitivity to

**Table 1:** Classification of the stages of chronic kidney disease\*<sup>5</sup>

Stage	Description	Glomerular filtration rate, mL/min/1.73 m <sup>2</sup>
1	Kidney damage† with normal or increased glomerular filtration rate	≥ 90
2	Kidney damage† with mild decreased glomerular filtration rate	60–89
3	Moderately decreased glomerular filtration rate	30–59
4	Severely decreased glomerular filtration rate	15–29
5	Kidney failure	< 15 (or dialysis)

\*Kidney damage or glomerular filtration rate less than 60 mL/min/1.73 m<sup>2</sup> for 3 or more months.

†Pathologic abnormalities or markers of damage, including persistent proteinuria, abnormalities in urine sediment (persistent presence of erythrocytes, erythrocyte casts, leukocytes or leukocyte casts) or abnormal results in imaging studies (evidence of scarring or small kidneys on ultrasound or bilateral cystic changes consistent with polycystic kidney disease).

conventional regimens, varying dietary advice and compliance issues related to the complexity of care required. Thus, it is important for clinicians to appreciate the importance of glycemic control for these patients.<sup>11–16</sup> At present there is limited evidence to guide recommendations for diabetic care in the chronic kidney disease population. As a consequence, the statements are limited in scope. These recommendations (Box 2) are not intended to replace the Canadian Diabetes Association Guidelines<sup>17</sup> but rather to focus on aspects of care specific to patients with chronic kidney disease. Additional information is available in the clinical practice guidelines from the Canadian Diabetes Association.<sup>17</sup>

Metformin is an inexpensive and effective oral hypoglycemic agent that is recommended as first-line therapy for both overweight and nonoverweight patients with type 2 diabetes mellitus.<sup>17</sup> Metformin has been shown to be effective in both obese and nonobese patients.<sup>18</sup> There is much concern about the safety of metformin in chronic kidney disease, particularly the risk for lactic acidosis. A Cochrane review of 206 trials including 47 846 patient-years of exposure to metformin found no cases of fatal or nonfatal lactic acidosis.<sup>19</sup> Reviews of case reports of metformin-associated lactic acidosis suggest metformin may be a coprecipitant of lactic acidosis, as cases were most commonly seen in acute (or acute on chronic) renal failure (often precipitated by angiotensin-converting-enzyme [ACE] inhibitors or nonsteroidal anti-inflammatory drugs), or

were associated with another major illness such as hepatic failure, sepsis, bowel obstruction and shock.<sup>20</sup>

### Dyslipidemia

There is a high prevalence of dyslipidemia among patients at every stage of chronic kidney disease.<sup>21</sup> Thus, screening, evaluation and therapeutic interventions for control of dyslipidemia are important. Unfortunately, because most clinical trials have excluded patients with chronic kidney disease, the evidentiary base is limited. Nonetheless, the guidelines attempt to address key questions related to lipid abnormalities in patients with chronic kidney disease (Box 3). Few data are available about the optimal frequency of lipid measurements in patients with chronic kidney disease; therefore, the working group recommends that existing guidelines for the general population be followed.<sup>22</sup> Subgroup analyses from landmark trials have demonstrated that statin therapy reduces the risk of cardiovascular

#### Box 1: Guidelines for the treatment of hypertension in patients with chronic kidney disease

##### Patients without diabetes

- For patients with proteinuric chronic kidney disease (urine ratio of albumin to creatinine  $\geq 30$  mg/mmol), antihypertensive therapy should include an ACE inhibitor (grade A) or an angiotensin-receptor blocker in cases of intolerance to ACE inhibitors (grade D).
- Blood pressure should be targeted to less than 130/80 mm Hg (grade C).
- For patients with nonproteinuric chronic kidney disease (albumin to creatinine ratio  $< 30$  mg/mmol), antihypertensive therapy should include either an ACE inhibitor (grade B), an angiotensin-receptor blocker (grade B), a thiazide diuretic (grade B), a  $\beta$ -blocker (patients aged 60 years or less; grade B) or a long-acting calcium-channel blocker (grade B).

##### Patients with diabetes

- Antihypertensive therapy should include either an ACE inhibitor (grade A) or an angiotensin-receptor blocker (grade A).
- Blood pressure should be targeted to less than 130 mm Hg systolic (grade C) and less than 80 mm Hg diastolic (grade B).

##### Patients with large-vessel renal vascular disease

- Renovascular hypertension should be treated in the same manner as for nondiabetic, nonproteinuric chronic kidney disease. Caution should be taken with the use of an ACE inhibitor or an angiotensin-receptor blocker because of the risk of acute renal failure (grade D).

Note: ACE = angiotensin-converting enzyme.

#### Box 2: Guidelines for the treatment of diabetes in patients with chronic kidney disease

##### Glycemic control

- Targets for glycemic control, where they can be achieved safely, should follow the Canadian Diabetes Association Guidelines (hemoglobin A<sub>1c</sub>  $< 7.0\%$ , fasting plasma glucose 4–7 mmol/L) (grade B).
- Glycemic control should be part of a multifactorial intervention strategy that addresses blood pressure control and cardiovascular risk, and promotes the use of ACE inhibitors, angiotensin-receptor blockers, statins and acetylsalicylic acid (grade A).

##### Use of metformin in type 2 diabetes mellitus

- Metformin is recommended for most patients with type 2 diabetes with stage 1 or 2 chronic kidney disease who have stable renal function that has been unchanged over the past 3 months (grade A).
- Metformin may be continued in patients with stable stage 3 chronic kidney disease (grade B).
- **Clinical practice recommendation:** Metformin should be stopped if there are acute changes in renal function or during periods of illnesses that could precipitate such changes (e.g., gastrointestinal upset or dehydration) or cause hypoxia (e.g., cardiac or respiratory failure). Particular care should be taken for patients also taking ACE inhibitors, angiotensin-receptor blockers, nonsteroidal anti-inflammatory drugs or diuretics, or after intravenous contrast administration because the risk of acute renal failure, and thus accumulation of lactic acid, is greatest for these patients.

##### Choice of other glucose-lowering agents

- Tailor the choice of other glucose-lowering agents (including insulin) to the individual patient, the level of renal function and comorbidity (grade D opinion).
- Risk of hypoglycemia should be assessed regularly for patients taking insulin or insulin secretagogues. These patients should be taught how to recognize, detect and treat hypoglycemia (grade D opinion).
- **Clinical practice recommendation:** Short-acting sulfonylureas (e.g., gliclazide) are preferred over long-acting agents for patients with chronic kidney disease.

Note: ACE = angiotensin-converting enzyme.

events in patients with stage 1–3 chronic kidney disease.<sup>23–25</sup> We therefore suggest that physicians prescribe statin therapy as per existing lipid guidelines. There is no evidence to support routine serial monitoring of creatinine kinase and alanine aminotransferase in patients with chronic kidney disease who are receiving low- to moderate-dose statin therapy.<sup>26–28</sup>

### Lifestyle management

This section of the guidelines stress the importance of lifestyle management in the care for patients with impaired renal function. Because chronic kidney disease shares common risk factors with cardiovascular disease and diabetes, lifestyle modifications directed at smoking, obesity, alcohol consumption, exercise and diet are important (Box 4). Dietary protein intake has been the focus of several trials. However, there is a lack of convincing evidence that the long-term restriction of protein intake (< 0.70 g/kg/day) delays the progression of chronic kidney disease. Thus, a protein-controlled diet (0.80–1.0 g/kg/day) is recommended.<sup>29–31</sup> There have been no studies about dietary salt restriction and development or progression of chronic kidney disease. However, the benefits of salt reduction as they pertain to the development and control of hypertension are available<sup>32,33</sup> and are included in the guidelines.

### Proteinuria

Proteinuria is included in the guidelines because it is a marker of kidney damage and an important risk factor for progression of chronic kidney disease as well as cardiovascular morbidity and mortality.<sup>34,35</sup> The presence of proteinuria in 2 of 3 consecutive urine samples is needed to determine persistent proteinuria at any glomerular filtration rate (Box 5). The preferred method of screening for proteinuria is a single random measurement of the ratio of urine protein to creatinine or of albumin to creatinine.<sup>36,37</sup> At present, population-based screening for proteinuria is not recommended. Both ACE inhibitors and angiotensin-receptor blockers are effective in reducing protein excretion.<sup>38–43</sup> Nonpharmacologic therapies are less effective.<sup>44,45</sup> The level of proteinuria at which ACE inhibitor or angiotensin-receptor blockers should be initiated has been defined for patients with hypertension (Box 1) and those with diabetes (Box 5). For patients without hypertension or diabetes, there is insufficient evidence to

determine the level of proteinuria at which to initiate therapy with an ACE inhibitor or an angiotensin-receptor blocker. However, a large trial showed benefit of ACE-inhibitor treat-

#### Box 3: Guidelines for the treatment of dyslipidemia in patients with chronic kidney disease

##### Screening

- A fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride) should be measured in adults with stage 1–3 chronic kidney disease (grade A).
- A fasting lipid profile should be measured in adults with stage 4 chronic kidney disease only if the results would influence the decision to initiate or alter lipid-modifying treatment (grade D).

##### Frequency of lipid-profile measurement

- Lipid profiles should be measured after an overnight fast (ideally  $\geq 12$  h duration) (grade A).
- Total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides should be measured (grade A).
- Fasting lipid profiles should be measured no sooner than 6 weeks after initiation or change in pharmacologic therapy. Thereafter, lipid profiles should be monitored every 6–12 months if the results could influence subsequent therapeutic decisions (grade D).

##### Treatment

- Statin therapy should be initiated for patients with stage 1–3 chronic kidney disease according to existing lipid guidelines for the general population (grade A).
- In patients with stage 1–3 chronic kidney disease, clinicians should consider titrating the dose of statin according to lipid guidelines for the general population (grade B).
- Clinicians should consider initiating statin therapy for patients with stage 4 chronic kidney disease and titrating the dose to achieve an LDL cholesterol level < 2.0 mmol/L and a ratio of total cholesterol to HDL cholesterol < 4.0 mmol/L (grade B).
- Gemfibrozil (1200 mg daily) may be considered as an alternative to statin treatment for patients with chronic kidney disease (stage 1–3) who are at intermediate or high cardiovascular risk with concomitant low levels of HDL cholesterol (< 1.0 mmol/L) (grade B).
- Fasting triglycerides > 10 mmol/L at any stage of chronic kidney disease should be treated by recommending lifestyle changes and adding gemfibrozil or niacin, as required to reduce the risk of acute pancreatitis (grade D). Current data do not support treating hypertriglyceridemia as a strategy to reduce cardiovascular risk (grade A).

##### Monitoring for medication adverse effects

- Serial monitoring of creatinine kinase and alanine aminotransferase is not required for asymptomatic patients with chronic kidney disease (any stage) taking a low to moderate dose of statin ( $\leq 20$  mg/d of simvastatin or atorvastatin, or an equivalent dose of another statin) (grade A).
- Serial creatinine kinase and alanine aminotransferase should be measured every 3 months for patients with stage 4 chronic kidney disease who are taking a moderate to high dose of statin ( $\geq 40$  mg/d of simvastatin or atorvastatin, or an equivalent dose of another statin) (grade D).
- A statin and fibrate should not be coadministered to patients with stage 4 chronic kidney disease because of the risk of rhabdomyolysis (grade D).
- Gemfibrozil is safe to use for patients with chronic kidney disease. Other fibrate preparations (e.g., fenofibrate) should be avoided or the dose significantly reduced for patients with stage 2–4 chronic kidney disease because of an increased risk of toxicity (grade D).

Note: ACE = angiotensin-converting enzyme, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

ment compared with conventional antihypertensive treatment among patients with 1 or more gram of proteinuria per day (protein to creatinine ratio about 100 mg/mmol).<sup>46,47</sup>

### Anemia

Anemia is prevalent among patients with an estimated glomerular filtration rate less than 60 mL/min/1.73 m<sup>2</sup>.<sup>48</sup> Anemia is associated with adverse outcomes in patients with chronic kidney disease, including hospital admission, cardiovascular disease and mortality.<sup>49,50</sup> Although erythropoietin deficiency is a well-known cause of anemia in this population, the guidelines recommend that other potential causes of anemia should be sought (eg., iron deficiency) and treated accordingly (Box 6). To date, therapies to normalize the hemoglobin level in these patients have not shown any health benefit. These therapies have been associated with an increased incidence of death or need for dialysis.<sup>51–53</sup> Based on this evidence, a target hemoglobin level of 110 g/L is recommended for patients with chronic kidney disease (acceptable range 100–120 g/L). The use of

erythropoiesis-stimulating agents for the treatment of anemia in patients with chronic kidney disease is associated with potential adverse outcomes, including increased blood pressure and thrombotic complications. They should be prescribed by a specialist with experience in prescribing these agents. Iron therapy is an important component of anemia management.<sup>54,55</sup> We recommend that the oral form of iron be considered preferentially over the intravenous form.

### Mineral metabolism

Renal excretory function plays an important role in maintaining the balance of calcium and phosphate. Because progressive chronic kidney disease results in the development of hyperphosphatemia and hypocalcemia, this section of the guidelines focuses on assessment and treatment of mineral abnormalities. These metabolic alterations may play a role in the pathophysiology of vascular calcification as well as bone disease. The potential for bone disease may be increased in the presence of acidosis, which may be treated with the use of oral bicarbonate.

The kidney is also a site of the 1 $\alpha$ -hydroxylation of 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D (calcitriol). As renal function declines in chronic kidney disease, calcitriol deficiency promotes parathyroid gland hyperplasia and increased parathyroid hormone synthesis, ultimately leading to secondary hyperparathyroidism.

Currently, there is limited evidence on the impact of mineral metabolism abnormalities or their treatment on outcomes in patients with chronic kidney disease not receiving dialysis. Our recommendations (Box 7) were primarily extrapolated from data obtained from patients receiving dialysis. Thus, the statements are limited in scope because of the need for an evidentiary base. Observational studies in the general and chronic kidney disease and dialysis populations suggest an association between such metabolic abnormalities in chronic kidney disease and mortality risk.<sup>56–58</sup> However, to date, there have been no randomized trials showing that improved metabolic control affects survival. In the absence of data supporting fracture or mortality reduction with metabolic control hard outcome, the working group considers best practice to be the maintenance of normal calcium and phosphate levels and supplementation with active vitamin D if parathyroid hormone levels are elevated. There is insufficient evidence to suggest routine measurement of 25-hydroxyvitamin D. Dietary modifications are recommended initially,<sup>59</sup> followed by therapy with calcium-containing

#### Box 4: Guidelines for lifestyle management for patients with chronic kidney disease

##### Smoking cessation

- Smoking cessation should be encouraged to reduce the risk of developing chronic kidney disease and end-stage renal disease, and to reduce the risk of cardiovascular disease (grade D).

##### Weight reduction

- Obese (BMI > 30.0 kg/m<sup>2</sup>) and overweight (BMI 25.0–29.9 kg/m<sup>2</sup>) people should be encouraged to reduce their BMI to lower their risk of chronic kidney disease and end-stage renal disease (grade D).
- Maintenance of a health body weight (BMI 18.5–24.9 kg/m<sup>2</sup>; waist circumference < 102 cm for men, < 88 cm for women) is recommended to prevent hypertension (grade C) or to reduce blood pressure in those with hypertension (grade B). All overweight people with hypertension should be advised to lose weight (grade B).

##### Dietary protein control

- A protein-controlled diet (0.80–1.0 g/kg/d) is recommended for adults with chronic kidney disease (grade D).
- Dietary protein restriction of < 0.70 g/kg/day should include careful monitoring of clinical and biochemical markers of nutritional deficiencies (grade D).

##### Alcohol intake

- To reduce blood pressure, alcohol consumption in both normotensive and hypertensive people should be in accordance with Canadian guidelines for low-risk drinking. Healthy adults should limit alcohol consumption to 2 drinks or less per day, and consumption should not exceed 14 standard drinks per week for men and 9 standard drinks per week for women (grade B).

##### Exercise

- People without hypertension (to reduce the possibility of becoming hypertensive) or those with hypertension (to lower their blood pressure) should be encouraged to accumulate 30–60 minutes of moderate-intensity dynamic exercise (walking, jogging, cycling or swimming) 4–7 days per week (grade D). Higher intensities of exercise are no more effective.

##### Dietary salt intake

- To prevent hypertension, a dietary sodium intake of < 100 mmol/day is recommended, in addition to a well-balanced diet (grade B).
- Patients with hypertension should limit their dietary sodium intake to 65–100 mmol/day (grade B).

Note: BMI = body mass index.

phosphate binders (calcium gluconate or calcium acetate). In the absence of data with morbidity and mortality reduction supporting phosphate binders that do not contain calcium (sevelamer and lanthanum), these agents cannot be recommended. In fact, the potential economic impact in Canada may be prohibitive.<sup>60</sup>

### Initiation of renal replacement therapy

Although the overall objectives of the guidelines and recommendations are to delay progression of both chronic kidney disease and its complications, a proportion of patients will require renal replacement therapy (either dialysis or transplantation) to extend their life. The purpose of this section of the guidelines is to delineate the aspects of education, care and processes that are necessary to optimize the preparation of these patients for renal replacement therapy (Box 8). Appendix 1 includes references with more complete information on this topic (available at [www.cmaj.ca/cgi/content/full/179/11/1154/DC1](http://www.cmaj.ca/cgi/content/full/179/11/1154/DC1)). Physicians and health care providers must be aware of the need for preparation and the time that is required to implement these care plans.

A kidney transplant from a live donor should be promoted as the first choice for eligible patients who require renal replacement therapy. Outcomes with deceased donor kidneys are also significantly better than with dialysis.<sup>61-63</sup> For patients with progressive chronic kidney disease with plans for hemodialysis, making plans for vascular access is an important component of their care in preparation for end-stage renal disease. Care plans may include detailed assessment (including venous mapping and avoidance of venipuncture or blood pressure measurements on the nondominant arm to protect it for access creation).<sup>64</sup> At this point, care should be coordinated by a nephrologist. A comprehensive discussion of monitoring of vascular access, prevention of infection and management of complications is included in the hemodialysis clinical practice guidelines by the Canadian Society of Nephrology.<sup>65</sup> More frequent or sustained dialysis, such as nocturnal hemodialysis or peritoneal dialysis, is an alternative to conventional hemodialysis received 3 times per week and should be offered to suitable patients based on need and availability.<sup>66</sup>

#### Box 5: Guidelines for the measurement and treatment of proteinuria in patients with chronic kidney disease

##### Measurement of proteinuria

- Screening for proteinuria should be performed for all patients who are at high risk of kidney disease (patients with diabetes, hypertension, vascular disease, autoimmune disease, estimated glomerular filtration rate < 60 mL/min/1.73m<sup>2</sup> or edema) (grade D, opinion).
- Screening should be performed by random urine samples to measure the ratio of protein to creatinine or of albumin to creatinine. For patients with diabetes, testing of the ratio of albumin to creatinine should be performed to screen for kidney disease (grade B).
- A ratio of protein to creatinine > 100 mg/mmol or a ratio of albumin to creatinine > 60 mg/mmol should be considered as thresholds to indicate high risk of progression to end-stage renal disease (grade D).

##### Treatment

- Adults with diabetes and persistent albuminuria (ratio of albumin to creatinine > 2.0 mg/mmol for men, > 2.8 mg/mmol for women) should receive an ACE inhibitor or an angiotensin-receptor blocker to delay the progression of chronic kidney disease (grade A).
- ACE inhibitors and angiotensin-receptor blockers are the drugs of choice for reducing proteinuria (grade A).
- In carefully selected patients, aldosterone-receptor antagonists may decrease proteinuria (grade D).
- Protein-controlled diet, as well as weight reduction (for patients with an elevated body mass index), may provide some benefit in decreasing proteinuria (grade D).

Note: ACE = angiotensin-converting enzyme.

#### Box 6: Guidelines for the treatment of anemia in patients with stage 3-5 chronic kidney disease

##### Assessment

- Anemia is defined as a hemoglobin level of < 135 g/L for adult men and < 120 g/L for adult women (grade D, opinion).

##### Initial evaluation

- Consider testing patients with a hemoglobin level < 120 g/L for the following (grade D, opinion): hemoglobin level, leukocyte count and differential, platelet count, erythrocyte indices, absolute reticulocyte count, serum ferritin and transferrin saturation.

##### Use of erythropoiesis-stimulating agents

- For patients with anemia and adequate iron stores, erythropoiesis-stimulating agents should be initiated if their hemoglobin level falls below 100 g/L (grade D, opinion).
- For patients receiving erythropoiesis-stimulating agents, the target hemoglobin level should be 110 g/L (grade A). An acceptable hemoglobin range is 100-120 g/L.
- Erythropoiesis-stimulating agents should be prescribed in conjunction with a specialist with experience in prescribing these agents (grade D, opinion).

##### Use of iron therapy

- For patients not receiving erythropoiesis-stimulating agents and who have a hemoglobin level < 110 g/L, iron should be administered to maintain a level of ferritin > 100 ng/mL and transferrin saturation > 20% (grade D).
- For patients receiving erythropoiesis-stimulating agents, iron should be administered to maintain a level of ferritin > 100 ng/mL and transferrin saturation > 20% (grade D).
- The oral form of iron is the preferred first-line therapy for patients with chronic kidney disease (grade D, opinion).
- Patients who do not achieve serum ferritin or transferrin saturation targets or both while taking the oral form of iron or who do not tolerate the oral form should receive the intravenous form of iron (grade D, opinion).

**Box 7: Guidelines for the assessment and treatment of mineral metabolism abnormalities in patients with chronic kidney disease****Assessment and therapeutic targets**

- Serum calcium, phosphate and parathyroid hormone levels should be measured for adults with stage 4 and 5 chronic kidney disease, and for adults with stage 3 chronic kidney disease and a progressive decline in renal function (grade D, opinion).
- Serum phosphate levels should be maintained within the normal range (grade C).
- Serum calcium levels should be maintained within the normal range (grade D).
- Intact parathyroid hormone levels may be elevated above normal values; the target level of serum intact parathyroid hormone is unknown (grade D, opinion).

**Treatment options**

- Dietary phosphate restriction should be used continuously to treat hyperphosphatemia (grade D).
- Therapy with calcium-containing phosphate binders (calcium carbonate or calcium acetate) should be initiated if dietary restriction fails to control hyperphosphatemia and if hypercalcemia is not present (grade D).
- If hypercalcemia develops, the dose of calcium-containing phosphate binders or vitamin D analogues should be reduced (grade D, opinion).
- Hypocalcemia should be corrected if the patient has symptoms or if it is associated with increasing parathyroid hormone levels (grade D, opinion).
- Consider prescribing vitamin-D analogues if serum levels of intact parathyroid hormone are  $> 53$  pmol/L. Therapy should be discontinued if hypercalcemia or hyperphosphatemia develops or if parathyroid hormone levels are  $< 10.6$  pmol/L. Vitamin-D analogues should be used in conjunction with a specialist with experience in prescribing these agents (grade D, opinion).
- There is insufficient evidence to recommend use of phosphate binders that do not contain calcium, novel vitamin-D analogues or calcimimetics (grade D, opinion).

**Box 8: Guidelines for preparation for initiation of renal replacement therapy for patients with chronic kidney disease****Components of care prior to initiation**

- If feasible, patients with an estimated GFR  $< 30$  mL/min/m<sup>2</sup> should receive care in a multidisciplinary setting that includes physicians, nurses, dietitians and social workers (grade C).
- A predialysis education program should include lifestyle modification, medication management, modality selection and vascular access as well as options for renal transplantation (grade D, opinion).

**Timing of initiation**

- No evidence currently exists upon which to recommend a GFR at which renal replacement therapy should be initiated in the absence of complications of chronic kidney disease (grade D, opinion).
- Patients with an estimated GFR  $< 20$  mL/min/m<sup>2</sup> may require initiation of renal replacement therapy if any of the following are present: symptoms of uremia (after excluding other causes), refractory metabolic complications (hyperkalemia, acidosis), volume overload (manifesting as resistant edema or hypertension) or a decline in nutritional status (as measured by serum albumin, lean body mass or Subjective Global Assessment) that is refractory to dietary intervention (grade D, opinion).
- A live-donor pre-emptive renal transplant should not be performed until the estimated GFR is  $< 20$  mL/min/m<sup>2</sup> and there is evidence of progressive and irreversible renal damage over the preceding 6–12 months (grade D, opinion).

Note: GFR = glomerular filtration rate.

**Comprehensive conservative management**

The care of patients with chronic kidney disease necessarily includes proactive comprehensive management for those who choose not to receive renal replacement therapy and for those who come to the end of their life after a period of time on a therapy. We describe the components and needs for comprehensive conservative management and end-of-life care for patients with chronic kidney disease (Box 9). We recognize that not all patients will have been referred to a nephrology team at the time that they declined renal replacement therapy, therefore, we have tried to be appropriately broad in these recommendations.

Comprehensive conservative management requires the involvement of an interdisciplinary team, including nephrologists, chronic kidney disease nurses, dietitian, social workers, psychologists, spiritual care workers, palliative care physicians and nurses, and appropriately trained and supervised volunteers. The patient's primary care physician is an integral part of this team.<sup>67</sup> In conjunction with the patient and family, the interdisciplinary team should develop a care plan that addresses the physical, psychological and spiritual needs of the patient and his or her family and caregivers. Shared decision-making is an integral component of this process, and revisions to the care plan should be based on the changing needs and preferences of the patient and family.<sup>68–70</sup>

**Future directions and knowledge gaps**

At present, the best available evidence suggests that blood pressure and glycemic control will have the greatest impact on delaying the progression of both chronic kidney disease and cardiovascular disease. Nonetheless, the complexity of this condition clearly requires a better understanding of the absolute and relative value of identifying and treating the myriad clinical and laboratory abnormalities that occur in the context of reduced kidney function. Although individual retrospective or observational studies and basic research have generated data that support the importance of anemia and lipid and mineral metabolism abnormalities, it is

### Box 9: Guidelines for comprehensive conservative management for patients with chronic kidney disease

#### Structure and process

- Renal programs and care providers for patients with progressive chronic kidney disease who choose not to pursue renal replacement therapies should ensure patients have access to an interdisciplinary team to provide comprehensive conservative management (grade D, opinion).

#### Advanced-care planning

- All chronic kidney disease programs and care providers should have a mechanism by which to develop documents and processes for advanced-care planning (grade D, opinion).

#### Components of comprehensive conservative management

- Comprehensive conservative management protocols should include symptom management, psychological care and spiritual care (grade D, opinion).

#### Care of the imminently dying patient

- Coordinated end-of-life care should be available to patients and families (grade D, opinion).

critical that we better define the importance of these conditions for each stage of chronic kidney disease. Furthermore, we need to develop and evaluate risk scores for progression, such that resources can be appropriately directed to patients at greatest risk of progression and not to those who simply have reduced kidney function or evidence of kidney damage.

We can identify patients at risk for chronic kidney disease who have cardiovascular disease, diabetes or belong to a specific ethnic group or have a family history of chronic kidney disease. We can ensure that patients with chronic kidney disease and any other risk factor for cardiovascular disease receive aggressive treatment, and that a sense of therapeutic nihilism does not overcome our judgment and clinical care. Most importantly, the lack of evidence should not foster further nihilism but rather encourage us to advocate for the design of and enrollment into randomized control trials that answer questions relevant to this population.

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Sheldon Tobe has received honoraria for academic talks for Pfizer, Bristol-Myers Squibb, Merck, Sanofi-Aventis, Amgen, Abbott, Boehringer Ingelheim, Bayer and AstraZeneca. He is involved in several contract and investigator-initiated research projects for Abbott, AstraZeneca, Pfizer, Ortho Biotech, Novartis, Bristol-Myers Squibb, Sanofi-Aventis, Amgen, Roche, Merck Frosst and Boehringer Ingelheim. Sheldon Tobe holds US and Canadian patents for a bicarbonate-buffered dialysis solution sold by Apotex/Dialysis Solutions Inc., and he works with this company as a consultant.

Philip McFarlane has been a consultant to or an advisory board member of Ortho Biotech, Amgen, Sanofi-Aventis, Bristol-Myers Squibb, Biovail, Pfizer, Novartis, AstraZeneca, Fresenius, Boehringer Ingelheim, Roche and Schering-Plough. He has received honoraria for presentations from Ortho-Biotech, Amgen, Sanofi-Aventis, Bristol-Myers Squibb, Biovail, Novartis, Abbott and Merck. Philip McFarlane has participated in or received research grant funding from Sanofi-Aventis, GlaxoSmithKline, Biovail, Boehringer Ingelheim, AstraZeneca, Ortho Biotech and Amgen.

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