Can J Diabetes 37 (2013) S129–S136

Contents lists available at SciVerse ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Clinical Practice Guidelines

Chronic Kidney Disease in Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Philip McFarlane MD, FRCPC, Richard E. Gilbert MBBS, PhD, FACP, FRACP, FRCPC, Lori MacCallum BScPhm, PharmD, Peter Senior MBBS, PhD, MRCP

KEY MESSAGES

- Identification of chronic kidney disease (CKD) in diabetes requires screening for proteinuria, as well as an assessment of renal function.
- All individuals with CKD should be considered at high risk for cardiovascular events and should be treated to reduce these risks.
- The progression of renal damage in diabetes can be slowed through intensive glycemic control and optimization of blood pressure. Progression of diabetic nephropathy can be slowed through the use of medications that disrupt the renin-angiotensin-aldosterone system.

PRACTICAL TIPS

Management of Potassium and Creatinine During the Use of Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin II Receptor Blocker (ARB) or Direct Renin Inhibitor (DRI)

- Check serum **potassium** and **creatinine** at baseline and within 1 to 2 weeks of initiation or titration of therapy AND during times of acute illness.
- If potassium becomes elevated or creatinine increases by more than 30% from baseline, therapy should be reviewed and serum creatinine and potassium levels should be rechecked.
- Mild-to-moderate stable hyperkalemia:
  - Counsel on a low-potassium diet.
  - If persistent, non–potassium-sparing diuretics and/or oral sodium bicarbonate (in those with a metabolic acidosis) should be considered.
  - Consider temporarily holding renin-angiotensin-aldosterone system (RAAS) blockade (i.e. ACE inhibitor, ARB or DRI).
- Severe hyperkalemia:
  - In addition to emergency management strategies, RAAS blockade should be held or discontinued.

Introduction

Diseases of the kidney are a common finding in people with diabetes, with up to half demonstrating signs of kidney damage in their lifetime (1–3). Diabetes is the leading cause of kidney disease in Canada (4). Kidney disease can be a particularly devastating complication, as it is associated with significant reductions in both length and quality of life (5,6). A variety of forms of kidney disease can be seen in people with diabetes, including diabetic nephropathy, ischemic damage related to vascular disease and hypertension, as well as other renal diseases that are unrelated to diabetes (Figure 1) (7,8). In this chapter, we will discuss how to screen for and diagnose chronic kidney disease (CKD) in people with diabetes, how to treat them with an aim to slow progression of CKD and discuss the impact of CKD on other aspects of diabetes management.

Diabetic Nephropathy

The classic description of diabetic nephropathy is of a progressive increase in proteinuria in people with longstanding diabetes followed by declining function that eventually can lead to end stage renal disease (ESRD) (Figure 2) (1,9,10). Key risk factors for diabetic nephropathy include long duration of diabetes, poor glycemic control, hypertension, male gender, obesity and cigarette smoking. Many of these factors are modifiable.

The earliest stage of diabetic nephropathy is hyperfiltration, where the glomerular filtration rate (GFR) is significantly higher than normal. Identification of hyperfiltration is not clinically useful, as it is difficult to determine from routine testing. Persistent albuminuria is considered the earliest clinical sign of diabetic nephropathy (Table 1). Initially, small amounts of albumin are leaked, below the detection threshold of a urine dipstick. This stage is referred to as “microalbuminuria.” This can worsen so that the urinary albumin excretion is sufficiently high to be detectable by a urine dipstick, a stage known as “overt nephropathy.” The rate of progression from normoalbuminuria to microalbuminuria then to overt nephropathy usually is slow, typically taking 5 years or longer to progress through each stage (11,12). During the early stages of diabetic nephropathy, the rate of loss of renal function is relatively slow (1 to 2 mL/min/1.73 m^2 per year) and not impressively higher than what is seen in the general population (0.5 to 1 mL/min/1.73 m^2 per year). However, late in the overt nephropathy phase, the rate of decline of renal function can accelerate (5 to 10 mL/min/1.73 m^2 per year). Thus, significant renal dysfunction is not usually seen until late in the course of diabetic nephropathy (13).

It is important to note that the rate of progression can vary between individuals, and that the clinical markers of the disease (i.e. estimated glomerular filtration rate [eGFR], urinary albumin

1499-2671/$ – see front matter
http://dx.doi.org/10.1016/j.jcjd.2013.01.037

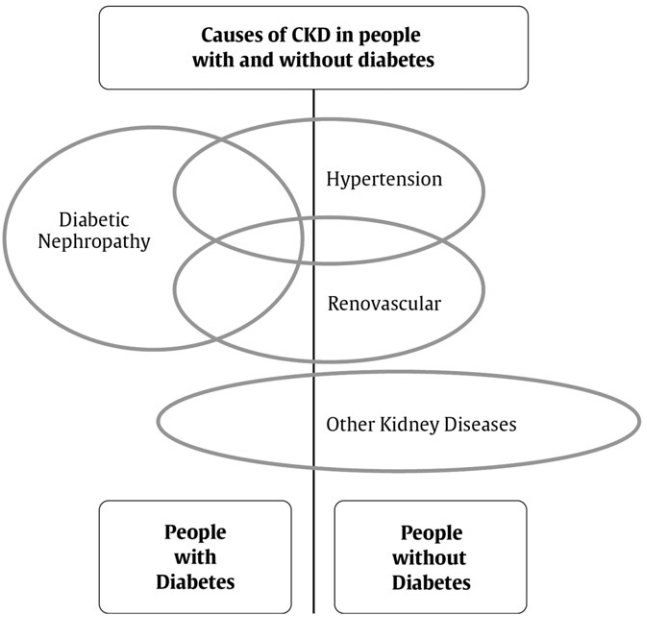

Figure 1. Causes of chronic kidney disease (CKD) in people with and without diabetes.

levels) do not always correlate well with the severity of renal disease seen on biopsy (14). Additionally, aggressive control of blood pressure (BP) and glycemia, and the use of renal protective drugs can slow or stop progression of diabetic nephropathy.

Other Kidney Diseases in People with Diabetes

People with diabetes (particularly type 2 diabetes) often develop kidney diseases other than diabetic nephropathy. Kidney biopsy series in type 2 diabetes have found that nondiabetic glomerular disease, particularly hypertensive or ischemic nephropathy, is as common as diabetic nephropathy in people with diabetes (7). In addition, there can be significant overlap (Figure 1). While these biopsy series are biased (biopsies are usually done in people with diabetes when nondiabetic renal disease is suspected), other studies have suggested that half of everyone with diabetes and significant kidney function impairment do not have albuminuria (15). These studies suggest that testing for albuminuria may be insufficient in identifying all patients with diabetes who have renal disease. In addition to measurements of urinary albumin excretion, estimations of the level of kidney function and urinalyses are required to identify patients with kidney disease other than diabetic nephropathy. In most cases, the risk of ESRD in diabetes does not appear to matter whether the renal diagnosis is one of diabetic nephropathy or an alternative diagnosis as management is the same (16). However, Table 2 lists some concerning clinical and laboratory features that would lead to suspicion of a kidney disease unrelated to diabetes, requiring such a person to undergo additional testing or referral (17–20).

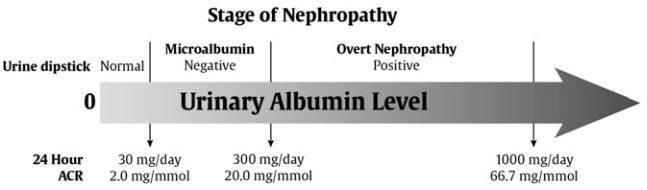

Figure 2. Level of urinary albumin by various test methods and stage of diabetic nephropathy. *ACR*, albumin-to-creatinine ratio.

Screening for Kidney Disease in People with Diabetes

Screening for kidney disease in people with diabetes involves an assessment of urinary albumin excretion and a measurement of the overall level of kidney function through an estimation of the GFR. Persistent abnormalities of either urinary albumin excretion or GFR, or significant urinalysis abnormalities, lead to the diagnosis of kidney disease in people with diabetes. People with type 1 diabetes are not expected to have kidney disease at the time of onset of diabetes, so screening can be delayed until the duration of diabetes exceeds 5 years. As the delay between onset and diagnosis of type 2 diabetes can be many years and as nondiabetic kidney disease is common, significant renal disease can be present at the time of diagnosis of type 2 diabetes (21,22), so screening should be initiated immediately at the time of diagnosis in this group.

Screening for Albuminuria

When screening for albuminuria, the test of choice is the random urine albumin-to-creatinine ratio (urinary ACR). The 24-hour urine collection for protein/albumin remains the gold standard; however, it is cumbersome to implement on a large scale and is often performed incorrectly (23–27). The random urine for albumin is insufficient, as the urinary albumin concentration can vary due to urine concentration (24). A random urine ACR predicts 24-hour urinary albumin excretion sufficiently well and is the test of choice for screening for albuminuria (23,25–27).

There is substantial day-to-day variability in albuminuria. In addition, transient increases in albuminuria can be provoked by a number of factors (Table 3) (28–32). When such conditions are present, screening for kidney disease should be delayed to avoid false positives. Furthermore, diagnosing a person as having albuminuria requires the elevated urinary albumin level to be persistent. At least 2 of 3 urine samples over time exhibiting elevations in urinary albumin levels are required before it is considered to be abnormal.

Estimation of GFR

The serum creatinine is the most common measurement of kidney function; however, it can inaccurately reflect renal function in many scenarios, particularly in extremes of patient age or size (33,34). Indeed, in people with diabetes, the GFR usually will be less than half of normal before the serum creatinine exceeds the lab normal range (35).

As mentioned, the 24-hour urine collection can be difficult to perform accurately. For this reason, a variety of methods have been developed to better estimate the level of glomerular filtration by combining the patient's serum creatinine with factors such as age, weight, and gender. The most common method of estimating renal function in Canada currently is the eGFR, using the 4-variable MDRD ("Modification of Diet in Renal Disease") equation (36). This equation requires knowledge of the patient's age, sex, serum creatinine and race and is automatically computed and reported by many labs whenever a serum creatinine is ordered. The MDRD eGFR performs well when the GFR is $<$60 mL/min (37) and despite its flaws is generally a better estimate of glomerular filtration than the serum creatinine value. Kidney diseases of all forms can be staged based on the degree of impairment of eGFR (Table 4).

The eGFR is useful for assessing chronic changes in renal function but should not be used in situations where kidney function is changing rapidly. Dehydration and other conditions that lead to intravascular volume contraction can lead to a transient decline in renal function. When such conditions are present, assessment of the level of kidney function may be clinically necessary but should

Table 1
Stages of diabetic nephropathy by level of urinary albumin level

Stages of Diabetic Nephropathy by Level of Urinary Albumin Level			
Stage of nephropathy	**Urine dipstick for protein**	**Urine ACR (mg/mmol)**	**24 hour urine collection for albumin**
Normal	Negative	<2	<30 mg/day
Microalbuminuria	Negative	2-20	30-300 mg/day
Overt nephropathy	Positive	>20 >67	>300 mg/day >1000 mg/day
Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels. ACR results may be elevated with conditions other than diabetic nephropathy (see text and Table 4)			

not be used to assess the stage of CKD. Because renal function can be transiently depressed, a persistent reduction in eGFR is required before it is considered to be abnormal.

Other Clinical Features and Urinary Abnormalities: When to Consider Additional Testing or Referral

Urinalysis findings of red blood cell casts are not a common finding in renal disease due to diabetes, and white blood cell casts or heme-granular casts are not compatible with a diagnosis of kidney disease due to diabetes. Although persistent microscopic hematuria can occur in about 20% of people with diabetic nephropathy, its presence should lead to the consideration of other urological or nephrological conditions. Table 2 lists other clinical clues that may point to a renal diagnosis other than kidney disease due to diabetes. Such patients should undergo an appropriate assessment for the cause of their disease. A rapid decline in eGFR or development of severe hypertension would suggest prompt referral to a specialist.

Although 24-hour collections are not needed for routine screening in diabetes, they can be useful when there is doubt about the accuracy of an eGFR, when screening for nonalbumin urinary proteins (e.g. multiple myeloma) or when estimating daily sodium intake in an individual with refractory edema or hypertension. Individuals should be counseled to discard the first morning urine on the day of collection and then collect all subsequent urine for a 24-hour period, including the first morning urine of the next day.

Screening Recommendations

People with diabetes should undergo annual screening for the presence of kidney disease when they are clinically stable and not suspected of having acute kidney injury or nondiabetic renal disease. Screening should be delayed in the presence of conditions that can cause transient albuminuria (Table 3) or a transient fall in eGFR.

Screening for CKD in people with diabetes should be performed with a random urine ACR and a serum creatinine that is then converted into an eGFR (Figure 3). This can be delayed 5 years from the onset of type 1 diabetes but should begin immediately at the time of diagnosis of type 2 diabetes. An abnormal screening test should be confirmed by repeat testing of the eGFR within 3 months, and 2 more random urine ACRs ordered during that interval. If either the eGFR remains low or at least 2 of the 3 random urine ACRs are abnormal, then a diagnosis of CKD is confirmed. The exception to this approach is when the random urine ACR indicates albuminuria in the overt nephropathy range, as this level of proteinuria rarely resolves spontaneously, so confirmatory testing is usually unnecessary.

Once a diagnosis of CKD has been made, a urine sample for dipstick and microscopy should be ordered. In the absence of any significant abnormalities other than proteinuria, then a presumptive diagnosis of kidney disease due to diabetes is made. The presence of clinical or laboratory abnormalities suggesting nondiabetic kidney disease indicates the need for appropriate workup or referral.

Prevention, Treatment and Follow Up

Optimal glycemic control established as soon as possible after diagnosis will reduce the risk of development of diabetic nephropathy (38–42). Optimal BP control also appears to be important in the prevention of diabetic nephropathy, although the results have been less consistent (41,43–45). Blockade of the renin-angiotensin-aldosterone system (RAAS) with either an

Table 2
Factors favouring the diagnosis of classical diabetic nephropathy or alternative renal diagnoses

Factors Favouring Classical Diabetic Nephropathy vs. Alternate Diagnoses (17-20)	
Favours Diabetic Nephropathy	**Favours Alternate Renal Diagnosis**
Persistent albuminuria	Extreme proteinuria (>6 g/d)
Bland urine sediment	Persistent hematuria (micro- or macroscopic) or active urinary sediment
Slow progression of disease	Rapidly falling eGFR
Low eGFR associated with overt proteinuria	Low eGFR with little or no proteinuria
Other complications of diabetes present	Other complications of diabetes not present or relatively not as severe
Know duration of DM >5 years	Known duration of diabetes <5 years
	Family history or nondiabetic renal disease (e.g. polycystic kidney disease)
	Signs or symptoms of systemic disease

Table 3
Conditions that can cause transient albuminuria

Potential Causes for Transient Albuminuria
Recent major exercise
Urinary tract infection
Febrile illness
Decompensated congestive heart failure
Menstruation
Acute severe elevation in blood glucose
Acute severe elevation in blood pressure

angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) can reduce the risk of diabetic nephropathy independent of their effect on BP. This protective effect has been demonstrated in people with diabetes and hypertension (46) but not in normotensive people with diabetes (47–49).

All people with CKD are at risk for cardiovascular (CV) events and should be treated to reduce these risks (see Vascular Protection chapter, p. S100) (50–52). The degree of risk of CV events or progression to ESRD increases as albuminuria levels rise, and as eGFR falls, with the combination of albuminuria and low eGFR predicting a very high level of risk (Figure 4) (53,54).

The progression of renal damage in diabetes can be slowed through intensive glycemic control (38) and optimization of BP (55). Progression of diabetic nephropathy can be slowed through the use of an ACE inhibitor or ARB (56), independent of their effect on BP, and these 2 medication classes appear to be equally effective for cardiorenal protection (57,58). In type 1 diabetes, ACE inhibitors have been shown to decrease albuminuria and prevent worsening of nephropathy (59), and ARBs have been shown to reduce proteinuria (60). In type 2 diabetes, ACE inhibitors and ARBs have been shown to decrease albuminuria and prevent worsening of nephropathy, and ARBs have been shown to delay the time to dialysis in those with renal dysfunction at baseline (61–64). In type 2 diabetes, ACE inhibitors have also been shown to reduce the chance of developing new nephropathy (46,61). These renal-protective effects also appear to be present in proteinuric individuals with diabetes and normal or near-normal BP. ACE inhibitors have been shown to reduce progression of diabetic nephropathy in albuminuric normotensive individuals with both type 1 (65–68) and type 2 diabetes (69).

Table 4
Stages of chronic kidney disease

Stages of Chronic Kidney Disease of all Types		
Stage	**Qualitative Description**	**Renal Function (mL/min/1.73 m²)**
1	Kidney damage-normal GFR	≥90
2	Kidney damage-mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	End-stage renal disease	<15 (or dialysis)

In CKD from causes other than diabetic nephropathy, ACE inhibition has been shown to reduce proteinuria, slow progressive loss of glomerular filtration rate and delay the need for dialysis (70,71). The issue of whether ARBs and ACE inhibitors are similarly effective in CKD that is not caused by diabetic nephropathy remains controversial (72,73).

A variety of strategies to more aggressively block the RAAS have been studied in kidney disease, including combining RAAS blockers or using very high doses of a single RAAS blocker. These strategies reduce proteinuria but have not been proven to improve patient outcomes in diabetic nephropathy (74–77) and come at a risk of increased acute renal failure, typically when a patient develops intravascular volume contraction (78). Aggressive RAAS blockade strategies should be restricted to specialized clinics.

Treating Kidney Disease Safely

The "sick day" medication list (see Appendix 7)

Several classes of medications used commonly in people with diabetes can reduce kidney function during periods of intercurrent illness and should be discontinued when patients are unwell, in particular when they develop significant intravascular volume contraction due to reduced oral intake or excessive losses due to vomiting or diarrhea. Diuretics can exacerbate intravascular volume contraction during periods of intercurrent illness. Blockers of the RAAS interfere with the kidney's response to intravascular volume contraction, namely, the ability of angiotensin II to contract the efferent arteriole to support glomerular filtration during these periods. Nonsteroidal anti-inflammatory drugs cause constriction of the afferent arterioles, which can further reduce blood flow into the glomerulus in patients who are volume contracted. For these reasons, all of these drugs can reduce kidney function during times of intercurrent illness. Consideration should be given to providing patients with a "sick day" medication list, instructing the patient to hold these medications if they feel that they are becoming dehydrated for any reason. A number of additional medications need to be dose adjusted in patients with renal dysfunction, so their usage and dosage should be reevaluated during periods where kidney function changes.

The safe use of RAAS blockers (ACE inhibitors, ARBs, and direct renin inhibitors [DRIs])

Drugs that block the RAAS reduce intraglomerular pressure, which, in turn, leads to a rise in serum creatinine of up to 30%, which then stabilizes (79). Although these drugs can be used safely in patients with renovascular disease, these patients may have an even larger rise in serum creatinine when these drugs are used (80–82). In the case of severe renovascular disease that is bilateral (or unilateral in a person with a single functioning kidney), RAAS blockade can precipitate renal failure. In addition, RAAS blockade can lead to hyperkalemia. For these reasons, the serum creatinine and potassium should be checked between 1 and 2 weeks after initiation or titration of a RAAS blocker (82). In patients in whom a significant change in creatinine or potassium is seen, further testing should be performed to ensure that these results have stabilized.

Mild-to-moderate hyperkalemia can be managed through dietary counselling, Diuretics, in particular furosemide, can increase urinary potassium excretion. Sodium bicarbonate (500 to 1300 mg orally twice a day) can also increase urinary potassium excretion, especially amongst individuals with a metabolic acidosis as demonstrated by a low serum bicarbonate level. If hyperkalemia is severe, RAAS blockade would need to be held or discontinued (83).

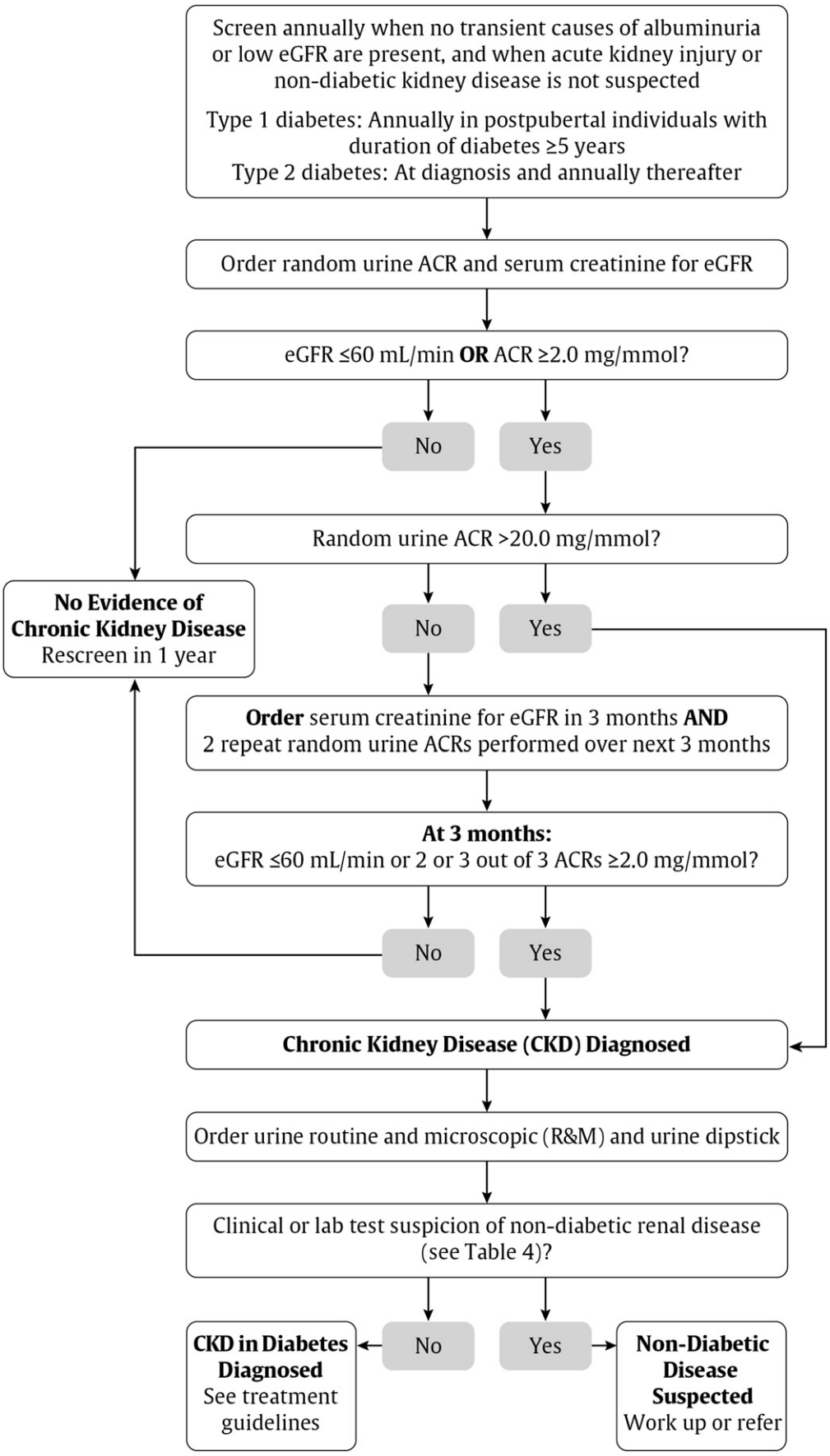

Figure 3. Screening for chronic kidney disease (CKD) in people with diabetes. *ACR*, albumin-to-creatinine ratio; *eGFR*, estimated glomerular filtration rate.

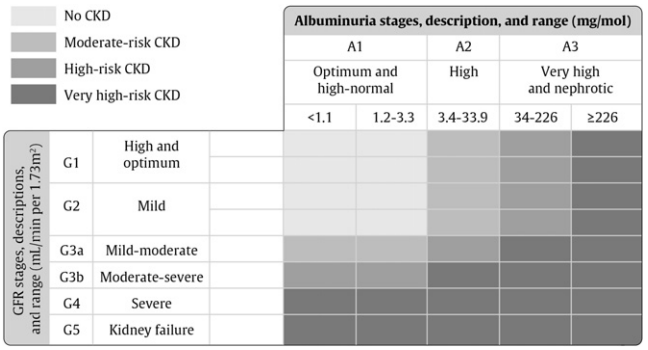

Figure 4. Relative risk of chronic kidney disease (CKD). Shading shows how adjusted relative risk is ranked for 5 outcomes from a meta-analysis of general population cohorts: all-cause mortality, cardiovascular mortality, kidney failure treated by dialysis and transplantation, acute kidney injury, and progression of kidney disease. *GFR*, glomerular filtration rate.

As the use of RAAS blockers during pregnancy has been associated with congenital malformations, women with diabetes of childbearing age should avoid pregnancy if drugs from these classes are required (84). If a woman with diabetes receiving such medications wishes to become pregnant, consideration should be given to their discontinuation prior to conception.

Medication selection and dosing in CKD

Many medications need to have their dose adjusted in the presence of low kidney function, and some are contraindicated in people with significant disease. Appendix 6 lists some medications commonly used in people with diabetes and how they should be used if kidney dysfunction is present.

Referral to a specialized renal clinic

Most people with CKD and diabetes will not require referral to a specialist in renal disease. However, specialist care may be necessary when renal dysfunction is severe, when there are difficulties implementing renal-protective strategies or when there are problems managing the sequelae of renal disease (85).

RECOMMENDATIONS

1. In adults, screening for CKD in diabetes should be conducted using a random urine ACR and a serum creatinine converted into an eGFR [Grade D, Consensus]. Screening should commence at diagnosis of diabetes in individuals with type 2 diabetes and 5 years after diagnosis in adults with type 1 diabetes and repeated yearly thereafter. A diagnosis of CKD should be made in patients with a random urine ACR $\geq$2.0 mg/mmol and/or an eGFR$<$60 mL/min on at least 2 of 3 samples over a 3-month period [Grade D, Consensus].

2. All patients with diabetes and CKD should receive a comprehensive, multifaceted approach to reduce cardiovascular risk (see Vascular Protection, p. S100) [Grade A, Level 1A (51,86)].

3. Adults with diabetes and CKD with either hypertension or albuminuria should receive an ACE inhibitor or an ARB to delay progression of CKD [Grade A, Level 1A for ACE inhibitor use in type 1 and type 2 diabetes, and for ARB use in type 2 diabetes; Grade D, Consensus, for ARB use in type 1 diabetes (59,61–65,68,69,87,88)].

4. People with diabetes on an ACE inhibitor or an ARB should have their serum creatinine and potassium levels checked at baseline and within 1 to 2 weeks of initiation or titration of therapy and during times of acute illness [Grade D, Consensus].

5. Adults with diabetes and CKD should be given a "sick day" medication list that outlines which medications should be held during times of acute illness (see Appendix, 7) [Grade D, Consensus].

6. Combination of agents that block the renin-angiotensin-aldosterone system (ACE inhibitor, ARB, DRI) should not be routinely used in the management of diabetes and CKD [Grade A, Level 1(89,90)].

7. People with diabetes should be referred to a nephrologist or internist with an expertise in CKD in the following situations:
   a. Chronic, progressive loss of kidney function
   b. ACR persistently $>$60 mg/mmol
   c. eGFR$<$30 mL/min
   d. Unable to remain on renal-protective therapies due to adverse effects such as hyperkalemia or $>$30% increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB
   e. Unable to achieve target BP (could be referred to any specialist in hypertension) [Grade D, Consensus]

Abbreviations:
ACE, angiotensin-converting enzyme; *ACR*, albumin-to-creatinine ratio; *ARB*, angiotensin II receptor block; *CKD*, chronic kidney disease; *DRI*, direct renin inhibitor.

Other Relevant Guidelines

Targets for Glycemic Control, p. S31
Monitoring Glycemic Control, p. S35
Pharmacotherapy in Type 1 Diabetes, p. S56
Pharmacologic Management of Type 2 Diabetes, p. S61
Type 1 Diabetes in Children and Adolescents, p. S153
Type 2 Diabetes in Children and Adolescents, p. S163
Diabetes and Pregnancy, p. S168
Diabetes in the Elderly, p. S184

Relevant Appendices

Appendix 6: Therapeutic Considerations for Renal Impairment
Appendix 7: Sick Day Medication List

References

1. Warram JH, Gearin G, Laffel L, et al. Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. J Am Soc Nephrol 1996;7:930–7.
2. Reenders K, de Nobel E, van den Hoogen HJ, et al. Diabetes and its long-term complications in general practice: a survey in a well-defined population. Fam Pract 1993;10:169–72.
3. Weir MR. Albuminuria predicting outcome in diabetes: incidence of microalbuminuria in Asia-Pacific Rim. Kidney Int 2004;66:S38–9.
4. Canadian Institute for Health Information. Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2000 to 2009. Ottawa, ON: Canada; 2011.
5. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32:S112–9.
6. Bell CM, Chapman RH, Stone PW, et al. An off-the-shelf help list: a comprehensive catalog of preference scores from published cost-utility analyses. Med Decision Making 2001;21:288–94.
7. Mazzucco G, Bertani T, Fortunato M, et al. Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies. Am J Kidney Dis 2002;39:713–20.
8. Gambara V, Mecca G, Remuzzi G, et al. Heterogeneous nature of renal lesions in type II diabetes. J Am Soc Nephrol 1993;3:1458–66.
9. Mathiesen ER, Ronn B, Storm B, et al. The natural course of microalbuminuria in insulin-dependent diabetes: a 10-year prospective study. Diabet Med 1995;12:482–7.
10. Lemley KV, Abdullah I, Myers BD, et al. Evolution of incipient nephropathy in type 2 diabetes mellitus. Kidney Int 2000;58:1228–37. Published erratum appears in Kidney Int. 2000;58:2257.
11. Gall MA, Nielsen FS, Smidt UM, et al. The course of kidney function in type 2 (non-insulin-dependent) diabetic patients with diabetic nephropathy. Diabetologia 1993;36:1071–8.
12. Jacobsen P, Rossing K, Tarnow L, et al. Progression of diabetic nephropathy in normotensive type 1 diabetic patients. Kidney Int Suppl 1999;71:S101–5.
13. Hasslacher C, Ritz E, Wahl P, et al. Similar risks of nephropathy in patients with type I or type II diabetes mellitus. Nephrol Dial Transplant 1989;4:859–63.
14. Biesenbach G, Bodlaj G, Pieringer H, et al. Clinical versus histological diagnosis of diabetic nephropathy: is renal biopsy required in type 2 diabetic patients with renal disease? QJM 2011;104:771–4.

15. Middleton RJ, Foley RN, Hegarty J, et al. The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol Dial Transplant 2006;21:88–92.
16. Ruggenenti P, Gambara V, Perna A, et al. The nephropathy of non-insulin-dependent diabetes: predictors of outcome relative to diverse patterns of renal injury. J Am Soc Nephrol 1998;9:2336–43.
17. VenkataRaman TV, Knickerbocker F, Sheldon CV. Unusual causes of renal failure in diabetics: two case studies. J Okla State Med Assoc 1990;83:164–8.
18. Anonymous. Clinical path conference. Unusual renal complications in diabetes mellitus. Minn Med 1967;50:387–93.
19. Amoah E, Glickman JL, Malchoff CD, et al. Clinical identification of nondiabetic renal disease in diabetic patients with type I and type II disease presenting with renal dysfunction. Am J Nephrol 1988;8:204–11.
20. El-Asrar AM, Al-Rubeaan KA, Al-Amro SA, et al. Retinopathy as a predictor of other diabetic complications. Int Ophthalmol 2001;24:1–11.
21. Ballard DJ, Humphrey LL, Melton LJ, et al. Epidemiology of persistent proteinuria in type II diabetes mellitus. Population-based study in Rochester, Minnesota. Diabetes 1988;37:405–12.
22. Winaver J, Teredesai P, Feldman HA, et al. Diabetic nephropathy as the mode of presentation of diabetes mellitus. Metab Clin Exp 1979;28:1023–30.
23. Ahn CW, Song YD, Kim JH, et al. The validity of random urine specimen albumin measurement as a screening test for diabetic nephropathy. Yonsei Med J 1999;40:40–5.
24. Kouri TT, Viikari JS, Mattila KS, et al. Microalbuminuria. Invalidity of simple concentration-based screening tests for early nephropathy due to urinary volumes of diabetic patients. Diabetes Care 1991;14:591–3.
25. Rodby RA, Rohde RD, Sharon Z, et al. The urine protein to creatinine ratio as a predictor of 24-hour urine protein excretion in type 1 diabetic patients with nephropathy. The Collaborative Study Group. Am J Kidney Dis 1995;26:904–9.
26. Chaiken RL, Khawaja R, Bard M, et al. Utility of untimed urinary albumin measurements in assessing albuminuria in black NIDDM subjects. Diabetes Care 1997;20:709–13.
27. Bakker AJ. Detection of microalbuminuria. Receiver operating characteristic curve analysis favors albumin-to-creatinine ratio over albumin concentration. Diabetes Care 1999;22:307–13.
28. Huttunen NP, Kaar M, Puukka R, et al. Exercise-induced proteinuria in children and adolescents with type 1 (insulin dependent) diabetes. Diabetologia 1981;21:495–7.
29. Solling J, Solling K, Mogensen CE. Patterns of proteinuria and circulating immune complexes in febrile patients. Acta Med Scand 1982;212:167–9.
30. Ritz E. Nephropathy in type 2 diabetes. J Intern Med 1999;245:111–26.
31. Wiseman M, Viberti G, Mackintosh D, et al. Glycaemia, arterial pressure and micro-albuminuria in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1984;26:401–5.
32. Ravid M, Savin H, Lang R, et al. Proteinuria, renal impairment, metabolic control, and blood pressure in type 2 diabetes mellitus. A 14-year follow-up report on 195 patients. Arch Intern Med 1992;152:1225–9.
33. Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine. Nephron 1992;62:249–56.
34. Bending JJ, Keen H, Viberti GC. Creatinine is a poor marker of renal failure. Diabet Med 1985;2:65–6.
35. Shemesh O, Golbetz H, Kriss JP, et al. Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int 1985;28:830–8.
36. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.
37. Poggio ED, Wang X, Greene T, et al. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 2005;16:459–66.
38. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. Lancet 1993;341:1306–9.
39. Anonymous. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. Kidney Int 1995;47:1703–20.
40. Anonymous. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–53.
41. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. N Eng J Med 2000;342:381–9.
42. Shichiri M, Kishikawa H, Ohkubo Y, et al. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000;23(Suppl 2):B21–9.
43. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703–13.
44. Schrier RW, Estacio RO, Mehler PS, et al. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. Nat Clin Pract Nephrol 2007;3:428–38.
45. de Galan BE, Perkovic V, Ninomiya T, et al. Lowering blood pressure reduces renal events in type 2 diabetes. J Am Soc Nephrol 2009;20:883–92.
46. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004;351:1941–51.
47. Chaturvedi N. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. Lancet 1997;349:1787–92.
48. Bilous R, Chaturvedi N, Sjolie AK, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. Ann Intern Med 2009;151:11–20. W13-W14.
49. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40–51.
50. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421–6.
51. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–93.
52. Gaede P, Vedel P, Parving HH, et al. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 1999;353:617–22.
53. Levey AS, Coresh J. Chronic kidney disease. Lancet 2012;379:165–80.
54. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089–100.
55. Maki DD, Ma JZ, Louis TA, et al. Long-term effects of antihypertensive agents on proteinuria and renal function. Arch Intern Med 1995;155:1073–80.
56. Kasiske BL, Kalil RS, Ma JZ, et al. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. Ann Intern Med 1993;118:129–38.
57. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004;351:1952–61.
58. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145–53.
59. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993;329:1456–62.
60. Andersen S, Tarnow L, Rossing P, et al. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. Kidney Int 2000;57:601–6.
61. Strippoli GF, Craig MC, Schena FP, et al. Role of blood pressure targets and specific antihypertensive agents used to prevent diabetic nephropathy and delay its progression. J Am Soc Nephrol 2006;17:S153–5.
62. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Eng J Med 2001;345:851–60.
63. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–9.
64. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870–8.
65. Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. Am J Med 1995;99:497–504.
66. Mathiesen ER, Hommel E, Giese J, et al. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. BMJ 1991;303:81–7.
67. Jerums G, Allen TJ, Campbell DJ, et al. Long-term comparison between perindopril and nifedipine in normotensive patients with type 1 diabetes and microalbuminuria. Am J Kidney Dis 2001;37:890–9.
68. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med 2001;134:370–9.
69. Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 1993;118:577–81.
70. Ruggenenti P, Perna A, Gherardi G, et al. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. Lancet 1998;352:1252–6.
71. Maschio G, Alberti D, Locatelli F, et al. Angiotensin-converting enzyme inhibitors and kidney protection: the AIPRI trial. The ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study Group. J Cardiovasc Pharmacol 1999;33(suppl 1):S16–20. discussion S41–S43.
72. Shoda J, Kanno Y, Suzuki H. A five-year comparison of the renal protective effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with non-diabetic nephropathy. Intern Med 2006;45:193–8.
73. Igarashi M, Hirata A, Kadomoto Y, et al. Dual blockade of angiotensin II with enalapril and losartan reduces proteinuria in hypertensive patients with type 2 diabetes. Endocr J 2006;53:493–501.
74. Jacobsen P, Parving HH. Beneficial impact on cardiovascular risk factors by dual blockade of the renin-angiotensin system in diabetic nephropathy. Kidney Int 2004;66:S108–10.

75. Burgess E, Muirhead N, Rene de Cotret P, et al. Supramaximal dose of candesartan in proteinuric renal disease. J Am Soc Nephrol 2009;20:893–900.
76. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol 2006;1:940–51.
77. Parving HH, Persson F, Lewis JB, et al. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008;358:2433–46.
78. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 2008;372:547–53.
79. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000;160:685–93.
80. Reams GP, Bauer JH, Gaddy P. Use of the converting enzyme inhibitor enalapril in renovascular hypertension. Effect on blood pressure, renal function, and the renin-angiotensin-aldosterone system. Hypertension 1986; 8:290–7.
81. Franklin SS, Smith RD. Comparison of effects of enalapril plus hydrochlorothiazide versus standard triple therapy on renal function in renovascular hypertension. Am J Med 1985;79:14–23.
82. Miyamori I, Yasuhara S, Takeda Y, et al. Effects of converting enzyme inhibition on split renal function in renovascular hypertension. Hypertension 1986;8: 415–21.
83. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med 2004;351:585–92.
84. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006; 354:2443–51.
85. Levin A, Mendelssohn D. Care and referral of adult patients with reduced kidney function: position paper from the Canadian Society of Nephrology. 2006.
86. Gaede P, Lund-Andersen H, Parving HH, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–91.
87. Mathiesen ER, Hommel E, Hansen HP, et al. Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. BMJ 1999; 319:24–5.
88. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. MicroAlbuminuria Reduction With VALsartan Study Investigators. Circulation 2002;106:672–8.
89. Tobe SW, Clase CM, Gao P, et al. Cardiovascular and renal outcomes with telmisartan, ramipril, or both in people at high renal risk: results from the ONTARGET and TRANSCEND studies. Circulation 2011;123:1098–107.
90. Parving H, Brenner BM, McMurray JJV, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012;367:2204–13.