# Chapter 4: Blood pressure management in CKD ND patients with diabetes mellitus

*Kidney International Supplements* (2012) **2,** 363–369; doi:10.1038/kisup.2012.54

## INTRODUCTION

This chapter addresses the management of BP in adult CKD patients (specifically non-dialysis-dependent CKD [CKD ND]) with diabetes mellitus. Previous guidelines[1,30] have used the term 'diabetic nephropathy' or 'diabetic kidney disease.' This Work Group decided to use the term 'diabetes with CKD' in recognition of the fact that many patients who have co-existing diabetes and CKD do not undergo kidney biopsy and may have other forms of kidney damage with or without the changes that characterize diabetes. Examples of alternative pathologies include nephroangiosclerosis, atheromatous embolism, atherosclerotic renal artery disease, or glomerulonephritis. In addition, there is evidence that the classic histological features of diabetic nephropathy can on occasion be found in patients who do not have a high urine albumin level.[194–196] Also, progressive loss of excretory kidney function has been observed in the absence of progression from microalbuminuria to overt proteinuria in some patients with diabetes.[197]

Observational studies in the general population provide strong evidence of a linear relationship between BP and risk of cardiovascular events.[21] A large number of RCTs have also shown that drugs that reduce BP also reduce the risk of subsequent cardiovascular events.[198] The benefits of BP reduction observed in clinical trials involving high-risk patients have also been shown to be consistent across a range of baseline BP levels in recent, large meta-analyses.[198,199] In addition, baseline BP levels have been shown to be a powerful determinant of the subsequent risk of kidney failure in large population-based studies from around the world.[148,200]

Diabetes increases the risk of CVD by a factor of two to three at every level of systolic BP,[201] and this risk is further potentiated by the presence of CKD. In addition, type 2 diabetes is a leading cause of CKD, accounting for 30 to 50% of new cases of kidney failure in the industrialized world.[202] Microalbuminuria is one of the earliest detectable manifestations of kidney disease in patients with diabetes, with a prevalence of 25% after 10 years of diabetes and an annual rate of progression to overt nephropathy of approximately 3%.[203] The risk of incident and progressive microalbuminuria is highly associated with BP levels.[204] Progression of retinopathy is also closely associated with high BP.[205–208] It is therefore important that the clinician is provided with clear, evidence-based recommendations on the use of BP-lowering drugs in the management of patients with diabetes and CKD. This management should also include interventions for multiple risk factors, which have been shown to improve outcomes in patients with diabetes.[209–211]

The Work Group recognizes that the benefits of BP reduction in patients with diabetes and CKD may include reductions of the risks of progressive loss of kidney function, CVD and progression of diabetic retinopathy. We also took into account the fact that the effects of BP reduction may differ among outcomes; for instance, a lower achieved BP may be associated with an increased risk of one outcome but a reduced risk of another.

These recommendations are not stratified by CKD stage as there are remarkably few studies in which the effect of BP-lowering therapy has been reported according to CKD stage. The Work Group could find no evidence that the balance of benefits and harms of BP-lowering therapy, or specific types of therapy, varied with the GFR—other than the known risks of hyperkalemia, particularly with agents that directly interfere with renin–angiotensin–aldosterone system (see Chapter 2).

**4.1: We recommend that adults with diabetes and CKD ND with urine albumin excretion $<30$ mg per 24 hours (or equivalent*) whose office BP is consistently $>140$ mm Hg systolic or $>90$ mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently $\leq 140$ mm Hg systolic and $\leq 90$ mm Hg diastolic. *(1B)***

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

## RATIONALE

- RCTs that have examined various BP targets or compared active treatment with placebo, along with observation studies, have been consistent in suggesting that lowering BP so that it is consistently $<140/90$ mm Hg will prevent major cardiovascular events. Lowering BP to these levels is also likely to reduce the risk of progressive CKD.
- The evidence for the benefit of further lowering of the BP target is mixed, with modest cardiovascular benefits in patients with diabetes partly offset by increases in the risk of serious adverse effects in trials, and inconsistency in results among observational studies using clinical trial datasets.

Recommendation 4.1 applies to diabetic patients with CKD, defined as a GFR $<60$ ml/min/1.73 $m^2$, and normal albumin excretion (normoalbuminuria) prior to the use of BP-lowering drugs such as ACE-Is or ARBs. Several studies have shown that this is not a rare occurrence in patients with type 2 diabetes.[195,196,212–217] For example, in the National Health and Nutrition Examination Survey (NHANES), 36% of adults with type 2 diabetes and a GFR $<60$ ml/min/1.73 $m^2$ had normal urine albumin levels.[195] A population-based study in Japan found 262 of 3297 people (7.9%) with type 2 diabetes and a GFR $<60$ ml/min/1.73 $m^2$ had a normal AER. The diabetic patients with CKD but a normal AER were older and included a higher proportion of women and patients with hypertension, hyperlipidemia, and CVD but fewer smokers, compared with the diabetic patients with a normal AER and preserved GFR.[217]

A long-term follow-up study of participants with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed that 24% of those who developed a GFR $<60$ ml/min/1.73 $m^2$ had an AER $<30$ mg per 24 hours at all previous evaluations,[218] indicating that normoalbuminuric CKD is also an important entity in type 1 diabetes.

***RCTs.*** The Work Group could not identify any RCTs in which patients with CKD and normoalbuminuric diabetes had been randomized to various BP targets. Several trials have been completed in broader populations with diabetes, some of whom had CKD at study entry. These are summarized here.

In the United Kingdom Prospective Diabetes Study (UKPDS) 38,[219] patients with diabetes, a minority of whom also had nephropathy, were randomized to BP $<150/85$ mm Hg or $<180/105$ mm Hg. Tighter BP control was associated with a reduction in risk of diabetes-related death, stroke, and progression of retinopathy.

The HOT study[220] recruited 18,790 adults with diastolic BP between 100 and 115 mm Hg and randomized them to one of three diastolic BP targets: $\leq 90$, $\leq 85$, and $\leq 80$ mm Hg. Among the 1501 subjects with diabetes (a relatively small proportion, suggesting under-representation of diabetics), the risk of major cardiovascular events in the group targeted to a diastolic BP $\leq 80$ mm Hg was half that of the group targeted to 90 mm Hg. Baseline data on cardiovascular risk factors were not provided for the diabetic subgroup, leading some commentators to speculate whether this result was due to imbalance between the groups rather than to a genuine treatment effect. No data were given on urinary albumin excretion in the diabetic subgroup.

The Appropriate Blood Pressure Control in Diabetes (ABCD) study was a 5-year prospective RCT comparing intensive and moderate BP control in patients with diabetes.[221] The hypertensive arm comprised diabetic patients with a diastolic BP $>90$ mm Hg randomized to a diastolic BP target of 75 mm Hg or 80 to 89 mm Hg. Patients assigned to the lower BP target were also randomized to receive either nisoldipine or enalapril. This arm of the trial was terminated early because of a significantly higher incidence of myocardial infarction (a pre-specified secondary end point) in the nisoldipine group.[222] At 5 years of follow-up, there was no difference in the rate of pre-specified kidney outcomes or cardiovascular outcomes between the group targeted to 75 mm Hg and the group targeted to 80 to 89 mm Hg but a significantly lower incidence of death in the 75 mm Hg group.[183]

The normotensive arm in the ABCD study comprised diabetic patients (around 30% of whom had CKD, as defined on the basis of albumin excretion) with a baseline BP $<140/90$ mm Hg who were randomized to placebo or active treatment (and in that group, further randomized to either enalapril or nisoldipine) titrated to reduce the diastolic BP to 10 mm Hg below baseline.[223] As compared with less-intensive treatment, intensive treatment (to the lower BP target) was not associated with any difference in the change in creatinine clearance over the study period but was associated with lower risks of progression from normoalbuminuria to microalbuminuria and from microalbuminuria to overt proteinuria, as well as a reduced risk of stroke and of progression of retinopathy. The inclusion criteria for the normotensive arm of ABCD prevents reliable extrapolation of this finding to patients whose baseline BP is $>140/90$ mm Hg.

The ACCORD study[159] randomized 4733 patients with diabetes and high cardiovascular risk to a systolic BP target $<140$ mm Hg or $<120$ mm Hg. A total of 39% of patients had an elevated urinary AER. There was no difference between the two groups in the primary composite end point (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death). However, the lower systolic BP target was associated with a significant reduction in the risk of stroke (62 events with $<140$ mm Hg target vs. 36 events with $<120$ mm Hg target, $P=0.01$), a pre-specified secondary end point, but also with a significant increase in rate of serious adverse events (30 events vs. 77 events, respectively; $P<0.001$).[224]

As compared with the group targeted to $<140$ mm Hg, the group targeted to $<120$ mm Hg had higher rates of hyperkalemia and elevations in SCr level. The mean GFR was significantly lower in the intensive-therapy (lower-target) group than in the standard-therapy group at the last visit. There were significantly more instances of a single GFR measurement $<30$ ml/min/1.73 $m^2$ in the intensive-therapy group than in the standard-therapy group (99 events vs. 52 events, respectively; $P<0.001$), but the proportion of participants with more than one GFR reading $<30$ ml/min/1.73 $m^2$ was similar in the two groups (38% vs. 32%, respectively; $P=0.46$). The frequency of macroalbuminuria at the final visit was significantly lower with intensive therapy than with standard therapy, and there was no between-group difference in the frequency of kidney failure or initiation of dialysis (in 58 patients vs. 59 patients, $P=0.93$).[159]

The ACCORD trial also showed that intensive glycemic control and combination lipid-lowering treatment, but not

intensive BP control, was associated with a reduction in the rate of progression of retinopathy.[224]

***Observational studies.*** There have been several large observational studies of patients with diabetes, CKD, or both, most of which found a lower risk of cardiovascular or kidney outcomes in people with lower BP.[148,225] These studies have been cited by many previous guidelines and used to support a BP target of $<130/80$ mm Hg for patients with CKD or diabetes. However, none of these studies prove causality and it is equally possible that higher BP, whether occurring before initiation of BP-lowering treatment or after, is simply a marker for more severe disease, which in turn has a poorer prognosis.[22]

Among patients screened for the Multiple Risk Factor Intervention (MRFIT) trial, there was a strong, graded, positive relationship between baseline BP and subsequent risk of kidney failure; the association was weaker among older men, blacks, and men with diabetes.[148] In the diabetic subgroup of MRFIT participants,[201] the risk of cardiovascular death increased to a greater degree with increasing risk factors, including systolic BP, than in the non-diabetic subgroup.

A strong association between baseline BP and subsequent risk of kidney failure was also demonstrated in an Okinawan study.[226] After adjustment for age and BMI, there was a significant, positive association between systolic BP and the risk of diabetic kidney failure, with a relationship also demonstrated for diastolic BP in women only.

The Pittsburg Epidemiology of Diabetes Complications (EDC) study[227] reported on 589 patients with childhood-onset diabetes. A graded association between baseline BP and subsequent risk of major events was found.

Data from the Cardiovascular Health Study and the Atherosclerosis Risk In Communities study[158] showed that among participants with CKD, there was a J-shaped relationship between systolic BP and risk of stroke, with a higher risk of stroke with a systolic BP $<120$ mm Hg; this relationship was not seen in those without CKD.

***Post hoc analyses of RCTs.*** *Post hoc* analyses of several large RCTs have indicated various relationships between achieved BP and outcomes.

A *post hoc* analysis of achieved BP and outcome in the Irbesartan Diabetic Nephropathy Trial (IDNT)[228] indicated that systolic BP $<120$ mm Hg was associated with an increased (rather than decreased) risk of cardiovascular events.

A *post hoc* analysis of UKPDS 36,[229] irrespective of treatment allocation, revealed a significant association between higher systolic BP and higher risk of clinical complications over a systolic BP range of 115 to 170 mm Hg.

The International Verapamil SR Trandolapril (INVEST) study recruited patients with hypertension and CAD and compared the effects of verapamil and atenolol. Trandolapril, hydrochlorothiazide, or both were added to achieve either a BP $<140/90$ mm Hg or a BP of $<130/85$ mm Hg in patients with diabetes or kidney impairment.[230] In an analysis of achieved BP among participants with diabetes (irrespective of their randomized treatment assignments), those who achieved tight BP control (i.e., a systolic BP $<130$ mm Hg) had similar rates of cardiovascular outcomes, and higher rates of death, than those with usual BP control (i.e., systolic BP, 130 to 140 mm Hg). Both groups had better outcomes than did a third group with poor BP control (i.e., systolic BP $>140$ mm Hg). The increased risk of mortality in the tight-control group persisted during an extended follow-up period.[231]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) collaborative group showed that the addition of perindopril plus indapamide to current therapy used in patients with type 2 diabetes and high cardiovascular risk reduced the rate of major or microvascular events.[232] In a secondary analysis, kidney events (mostly measures of appearance or worsening of urinary AER) were less frequent with a lower achieved BP at the follow-up visit.[233] The absolute risk reductions for cardiovascular and kidney end points associated with active treatment (irrespective of BP) were greater among patients with CKD 3–5 than among patients with CKD 1–2.[234]

***Interpretation.*** The Work Group believed that the data for reducing usual systolic BP to $\leq 140$ mm Hg and diastolic BP to $\leq 90$ mm Hg were strong, on the basis of the data presented above, as well as the clear relationship between BP levels and the risk of cardiovascular and kidney outcomes consistently noted in observational studies in both the general population[21,198,199] and in patients with diabetes with a systolic BP $>140$ mm Hg and a diastolic BP $>90$ mm Hg.[229,233] Further support is provided by reports from a number of clinical trials or trial subgroups demonstrating that BP-lowering therapy prevents cardiovascular and kidney events in patients with diabetes, most of whom had BP levels $>140/90$ mm Hg at trial entry.[183,219,221,223,232] There are few data for individuals with diabetes and CKD, but those that are available have reported broadly consistent findings.[234]

The Work Group does not believe that the evidence is sufficiently strong to support a lower target BP level for all patients with diabetes and CKD. Some support for lower BP targets is provided by the ACCORD and ABCD trials population. However in ACCORD, these benefits must be balanced against the increased risk of adverse events. As a result, it was felt that the risk-to-benefit ratio is likely to be unfavorable for at least some groups of individuals with diabetes and CKD. These include patients with diabetes and non-albuminuric CKD, who may be likely to have additional co-morbidities; the elderly, who are prone to falls; patients with marked systolic hypertension; and those with severe autonomic neuropathy. Such patients may have been underrepresented in the RCTs and observational studies.

A target BP of $\leq 140$ systolic and $\leq 90$ mm Hg diastolic may appear to require less aggressive therapy than the targets recommended in some other guidelines for patients with diabetes. However, whether this is true depends on how targets are interpreted by clinicians. There is extensive evidence from routine clinical practice that many patients do not achieve the targets set in guidelines; instead, achieved

values often have a normal distribution around the target.[22] This distribution of values is the reason for the wording we have chosen for the recommendation statements: that BP be "consistently" below a given level. For instance, to account for random fluctuations in resting office BP over time, the intervention threshold needs to be significantly $<130$ mm Hg to achieve a systolic BP consistently $<130$ mm Hg.

The Work Group, therefore, is confident that most individuals with diabetes and CKD should have their usual BP lowered to be consistently $\leq 140/90$ mm Hg (hence the grade of 1B for recommendation 4.1), and that targets lower than $\leq 140/90$ mm Hg could be considered on an individual basis for patients believed to be more likely to benefit than to be harmed by the treatment (e.g., patients not already on several BP-lowering agents, younger individuals, or persons at high risk of stroke).

Overall, the evidence supporting the statement that systolic BP should be lowered to $\leq 140$ mm Hg is at least level B. However, the evidence supporting the implication that systolic BP needs to be lowered further, for instance to $\leq 130$ mm Hg, is weaker. This grading should not, therefore, be taken to imply that no further research is required on the question of lower BP targets in this group.

***Comparison with current guidelines.*** Recommendation 4.1 is consistent with recommendations made by numerous international and national guidelines for the general population,[9,30,235–244] all of which agree on a treatment goal of $\leq 140/90$ mm Hg on the grounds that BP-lowering drugs reduce the risk of all-cause and cardiovascular mortality in people whose BP is $>140/90$ mm Hg. There is no reason to expect that patients with diabetes and CKD are less likely to have a benefit. Although there is observational evidence that the risk of CVD is higher among diabetic patients than non-diabetic patients at any given BP, these findings do not, in the absence of RCT evidence, support a recommendation that BP should be lowered further than is recommended in diabetic patients.

The Work Group is aware that this recommendation appears more conservative than the recommendations of some other international and national guidelines that recommend a BP target $\leq 130/80$ mm Hg for patients with diabetes and CKD.[1,9,30,237–240,243,245–247] However, there is insufficient high-quality evidence from RCTs to support a lower target for patients with diabetes and CKD (which we defined as a GFR $<60$ ml/min/1.73 m$^2$) who do not have an increased urinary AER. All other guidelines have relied on observational evidence to support a lower systolic BP threshold for patients with diabetes. The Work Group did not consider the evidence from the HOT[220] and ABCD[221] trials strong enough to justify a recommendation to lower the target diastolic BP to $\leq 80$ mm Hg.

The Work Group analyzed the evidence base for the existing guidelines carefully to ensure that the apparent departure from accepted wisdom was justified. Few existing guidelines specify how patients with normoalbuminuric CKD and diabetes should be treated with BP-lowering drugs, with the majority advising a BP target of $\leq 130/80$ mm Hg for all patients with diabetes, irrespective of GFR or albuminuria. Although the grades (and grading system) of these recommendations vary, all supporting statements acknowledge that the evidence is largely observational. For instance, many guidelines refer back to JNC 7,[9] which qualified the recommendation with the caveat, 'although available data are somewhat sparse to justify the low target level of 130/80 mm Hg ….' The JNC 7 goes on to cite the American Diabetes Association guidelines[245] and the supporting literature analysis,[235] which rely on the HOT findings[220] for justification of the 80 mm Hg diastolic BP target[245] and on Systolic Hypertension in the Elderly Program (SHEP)[151] and Systolic Hypertension in Europe (Syst-Eur) trial[248] (both studies of the general population) for the 140 mm Hg systolic BP target. Finally, the JNC 7 states that 'Epidemiological studies indicate that there is a benefit to reducing systolic BP still further to 130 mm Hg or below', citing two references, UKPDS 36[229] and a study from Allegheny County that contains no data on BP.[249]

We have not made recommendations about the choice of the BP-lowering drug to be used in patients with CKD and diabetes who do not have elevated rates of urinary albumin excretion. Although there is some evidence that inhibitors of the renin–angiotensin system might prevent an increase in urinary AER,[250,251] particularly in the presence of higher BP,[252] and might also reduce cardiovascular risk, such studies have not been performed in patients with reduced GFR but normal urinary albumin excretion. In such patients, the balance of risks and benefits of the use of ACE-Is or ARBs may well differ from the balance of their use for primary prevention of diabetic kidney disease.

***Considerations.*** Most interpretations of the observational evidence predict that achieved BPs below a target of $\leq 140/90$ mm Hg in patients with CKD and diabetes would be associated with additional benefit in the prevention of both progressive kidney disease and cardiovascular events. However, no RCTs have demonstrated such a benefit. It remains possible that clinical harm could be done, at least in some subgroups, by attempting to reach lower BPs. Achieving lower BPs would require multiple drug treatments in the majority of patients with CKD and diabetes, particularly those with high pulse pressures. This has implications both for adherence and for the cost of treatment, of which the latter is particularly important in resource-poor settings.

**4.2: We suggest that adults with diabetes and CKD ND with urine albumin excretion $>30$ mg per 24 hours (or equivalent*) whose office BP is consistently $>130$ mm Hg systolic or $>80$ mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently $\leq 130$ mm Hg systolic and $\leq 80$ mm Hg diastolic. *(2D)***

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

**RATIONALE**

- Observational studies show that the level of urine albumin predicts the risk of adverse cardiovascular and kidney outcomes.
- BP lowering reduces the rate of urinary albumin excretion, which may in turn lead to a reduced risk of both kidney and cardiovascular events, although this has not been shown in RCTs.

***RCTs.*** The Work Group found only one RCT, from the Steno Diabetes Centre in Copenhagen (Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria [Steno-2 study]) in which diabetic patients with high urine albumin were selected and randomized to two BP targets.[209,211,253] In the Steno-2 study, 160 adults with microalbuminuria and type 2 diabetes were randomized to intensive multifactorial intervention or to conventional therapy. The intensive-care arm received ACE-I or ARB irrespective of BP and had a BP target that was initially 140/85 mm Hg but was reduced to 130/80 mm Hg during the study, as compared to $<160/95$ mm Hg which was subsequently reduced to $<135/85$ mm Hg in the conventional arm. However, intensive intervention also included dietary advice, exercise, lipid-lowering treatment, help with smoking cessation, vitamin supplementation, aspirin, and intensified glycemic control. This intensive therapy was shown to be associated with a reduced risk of CVD, nephropathy, retinopathy, and autonomic neuropathy. The improvements seen in the intensive-therapy group were mostly in BP and the lipid profile, with only minor differences between the two groups in glycemic control and no differences in smoking, exercise measures, or body weight.[209]

***Observational evidence.*** There is strong observational evidence of an association between higher BP and an increased risk of worsening kidney function.[148,201,225,254,255] Diabetic patients with microalbuminuria are at increased risk of both CVD[256] and progressive kidney disease as compared to diabetic patients with normal albumin excretion.[256–258] Reduction of the rate of urinary albumin excretion during treatment is associated with a better kidney and cardiovascular prognosis.[210,250,259–261] However, these associations do not prove causation, and it remains possible, albeit highly unlikely, that patients in whom the rate of urine albumin excretion declines, either spontaneously or in response to treatment, have intrinsically less severe disease than those in whom no remission occurs. RCTs examining the effects of targeting certain levels of urine albumin on clinically relevant end points are needed before it can be concluded that treatment to reduce the rate of urinary albumin excretion will improve prognosis.

The Work Group therefore felt that benefits of targeting lower BP levels were likely to be greater for individuals with micro- or macroalbuminuria, so a target BP of $\leq 130/80$ mm Hg is suggested; however, stronger evidence is required in this population, hence the grade of 2D.

### 4.3: We suggest that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). *(2D)*

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

**RATIONALE**

- Patients with diabetes and microalbuminuria are at increased risk of kidney failure and cardiovascular events.
- ACE-Is and ARBs reduce the level of urine albumin in patients with diabetes and microalbuminuria at baseline, but data regarding the effects on kidney failure or cardiovascular outcomes are limited.

Microalbuminuria is much more common than frank proteinuria or albuminuria in patients with diabetes, but it is also associated with an increased risk of kidney and cardiovascular events. Several trials have shown a benefit of ACE-Is or ARBs over placebo in patients with microalbuminuria, irrespective of pre-treatment BP (See Supplementary Tables 37–42 online).[180,181,262–267] All of these trials studied the effects of treatment on surrogate outcomes, most commonly the transition to overt proteinuria; none demonstrate conclusively that these improvements are associated with a reduction in hard end points in this population, although this may be the result of low event rates, inadequate statistical power, and short follow-up times. The Work Group believes that ACE-Is and ARBs should be the preferred classes of BP-lowering agent used in patients with diabetes and microalbuminuria, although the relatively weak available evidence is reflected in the poor grade assigned to this guideline statement (2D).

We have not made statements about prevention of microalbuminuria as this topic will be addressed in the forthcoming KDOQI Diabetes guideline update.[268]

### 4.4: We recommend that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion $>300$ mg per 24 hours (or equivalent*). *(1B)*

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1.

**RATIONALE**

- Patients with diabetes and high levels of urine albumin are at a particularly high risk of adverse cardiovascular and kidney outcomes.
- There is strong evidence from RCTs conducted in patients with diabetes and CKD demonstrating that ACE-Is and ARBs protect against kidney failure and increases in albumin levels.

Individuals with elevated levels of urinary albumin or protein and diabetes have some of the highest rates of cardiovascular events and kidney failure of any group with CKD. For

example, in IDNT and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, the annual risk of the kidney and cardiovascular end points all approached 10%.[182,184,259–261]

***RCTs.*** Several RCTs have provided high-quality evidence, both in type 1 diabetes[269] and type 2 diabetes,[182,184] that ARBs and ACE-Is reduce the risk of kidney outcomes[270] as compared to placebo or a dihydropyridine calcium-channel blocker,[184] although no clear effect on cardiovascular outcomes has been established (possibly due to inadequate power) (see Supplementary Tables 37–42 online). However, applicability of study findings to the entire CKD and diabetes population is somewhat limited, because major studies have excluded patients with clinically significant CVD. There is high-quality evidence from trials of high-risk individuals from the general population showing that ARBs and ACE-Is improve cardiovascular outcomes,[185,271–276] including in patients with diabetes.[277,278] But these studies did not focus on patients with clinically significant albuminuria. In contrast, there was no benefit of ACE-Is as compared to diuretic therapy in the CKD and diabetic subgroups in ALLHAT,[279] although, again, few of the study patients were likely to have had frank albuminuria. Moreover, ALLHAT showed clear BP differences in favor of diuretic therapy over ACE-Is, making the comparison between the two groups somewhat difficult. As the RCT data in this population is strong and consistent, the level of evidence is high (see Supplementary Table 37 online). The decision on the grade of this recommendation statement (1B) was made by a majority vote. The minority of Work Group members supported an evidence grade of A.

The choice between an ACE-I and an ARB in CKD patients is controversial. In general, the evidence for kidney outcomes that supports the use of ACE-Is is older and applies largely to type 1 diabetes, whereas the evidence supporting the use of ARB comes from more recent trials in type 2 diabetes. For cardiovascular protection in patients with diabetes, the evidence largely points to ACE-Is. The available data are consistent, suggesting the effects of both classes of agents are likely to be similar. Cost and availability may be an important consideration in some countries. However, extrapolations within and between drug classes must be made with care: within-class effects on hard outcomes may differ substantially and may depend on the dose, making extrapolation to other drug classes problematic. A 2004 meta-analysis concluded that there was insufficient evidence on the relative effects of ACE-Is versus ARBs on survival.[280] We were unable to find trials directly comparing ACE-Is and ARBs in patients with diabetes and albuminuria. No clear difference between the effects of the two classes of drugs was found in the large Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) trial involving people at high cardiovascular risk, including subgroups with diabetes or CKD.[281,282] However, this study was not powered to make this comparison, so a real difference remains possible.

The data are even more scarce regarding the effects of other drug classes on outcomes in patients with diabetes and proteinuria. In IDNT, patients with proteinuria were randomized to irbesartan, amlodipine, or placebo. Amlodipine did not significantly affect the risk of kidney or cardiovascular events as compared to placebo and was clearly inferior to irbesartan for the prevention of kidney outcomes.[184] Aldosterone antagonists can reduce the risk of proteinuria in non-diabetic CKD patients[109,283] and in patients with diabetic nephropathy,[108] but adequately powered studies are lacking.

In the opinion of the Work Group, ACE-Is and ARBs are likely to be similarly effective in improving outcomes in patients with diabetes and proteinuria. Practitioners should therefore base prescribing decisions on the evidence available for each class, the risk of side effects, and cost considerations.

## RESEARCH RECOMMENDATIONS

- Prospective RCTs of a risk-based approach to the reduction of cardiovascular risk and kidney end points are encouraged.
- Studies comparing various BP intervention thresholds and targets among patients with diabetes, with or without an increased urinary AER, and with or without a reduced GFR are needed.
- Studies in which drug dose is titrated on the basis of the urine albumin level (or change in GFR) are needed.
- Studies on the effects of non-dihydropyridine calcium-channel blockers on long-term outcomes are needed.
- Prospective studies of add-on therapy (consisting of thiazides, aldosterone antagonists, or DRIs) and reduction of sodium chloride intake on the effects of ACE-Is or ARBs in patients with diabetes and CKD are encouraged.
- Prospective studies of the combination of ACE-Is and ARBs in patients with diabetes and CKD are encouraged.
- Prospective studies of different target BP levels stratified by GFR are encouraged.

## DISCLAIMER

**SUPPLEMENTARY MATERIAL**

*Supplementary Table 37*. Evidence profile of RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD and DM.

*Supplementary Table 38*. RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD and DM [categorical outcomes].

*Supplementary Table 39*. RCTs examining the effect of ACEI or ARB vs. placebo in patient with CKD and DM [continuous outcomes].

*Supplementary Table 40*. Evidence profile of RCTs examining the effect of ACEI or ARB vs. dihydropyridine CCB in patients with CKD and Type 2 DM.

*Supplementary Table 41*. RCTs examining the effect of ACEI or ARB vs. dihydropyridine CCB in patients with CKD and Type 2 DM [categorical outcomes].

*Supplementary Table 42*. RCTs examining the effect of ACEI or ARB vs. dihydropyridine CCB in patients with CKD and Type 2 DM [continuous outcomes].

*Supplementary Table 43*. Evidence profile of RCTs examining the effect of ACEI vs. ARB in patients with Type 2 DKD.

*Supplementary Table 44*. RCTs examining the effect of ACEI vs. ARB in microalbuminuric patients with CKD and Type 2 DM [categorical outcomes].

*Supplementary Table 45*. RCTs examining the effect of ACEI vs. ARB in microalbuminuric patients with CKD and Type 2 DM [continuous outcomes].

*Supplementary Table 46*. Evidence profile of RCTs examining the effect of ARB vs. ARB in patients with CKD and DM.

*Supplementary Table 47*. RCTs examining the effect of ARB vs. ARB in overtly albuminuric patients with CKD and Type 2 DM [categorical outcomes].

*Supplementary Table 48*. RCTs examining the effect of ARB vs. ARB in overtly albuminuric patients with CKD and Type 2 DM [continuous outcomes].

*Supplementary Table 49*. RCTs examining the effect of DRI + ARB vs. placebo + ARB in microalbuminuric patients with CKD and Type 2 DM [continuous outcomes].

*Supplementary Table 50*. RCTs examining the effect of dihydropyridine CCB vs. placebo in overtly albuminuric patients with CKD and Type 2 DM [categorical outcomes].

*Supplementary Table 51*. RCTs examining the effect of aldosterone antagonist + ACEI vs. placebo + ACEI in patients with CKD and Type 2 DM [continuous outcomes].

*Supplementary Table 52*. RCTs examining the effect of endothelin antagonist vs. endothelin antagonist in patients with CKD with Type 2 DM [categorical outcomes].

*Supplementary Table 53*. RCTs examining the effect of endothelin antagonist vs. endothelin antagonist in patients with CKD with Type 2 DM [continuous outcomes].

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/bp.php