Published in final edited form as:
Am J Kidney Dis. 2010 March ; 55(3): 426–430. doi:10.1053/j.ajkd.2009.10.001.

Prevention of Diabetic Kidney Disease: Negative Clinical Trials with Renin-Angiotensin System Inhibitors

Robert G. Nelson, MD, PhD[1] and **Katherine R. Tuttle, MD**[2]

[1]Diabetes Epidemiology and Clinical Research Section, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona

[2]Providence Medical Research Center at Sacred Heart Medical Center and Children's Hospital, University of Washington School of Medicine, Spokane and Seattle, Washington

The onset of diabetic kidney disease (DKD) is typically marked by development of increased urinary albumin excretion. Microalbuminuria, the earliest detectable increase in urinary albumin, is defined by an albumin-to-creatinine ratio in the range of 30–300 mg/g [1]. Although there is currently a debate about whether albuminuria is an adequate biomarker of DKD, it remains the test most commonly used by clinicians and researchers alike to screen for DKD. Since angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are proven therapies for DKD characterized by macroalbuminuria (albumin-to-creatinine ratio >300 mg/g), by logical extension these agents might also prevent the development of microalbuminuria. Two recent publications test this hypothesis [2, 3].

WHAT DO THESE IMPORTANT STUDIES SHOW?

Diabetic Retinopathy Candesartan Trials Renal (DIRECT-Renal) Program

The DIRECT-Renal Program [2] pooled three related randomized double-blinded placebo-controlled clinical trials to assess whether the ARB candesartan prevents the onset of microalbuminuria and diminishes the rate of change of urinary albumin excretion in patients with type 1 or type 2 diabetes. Of the 5,231 diabetic participants in DIRECT-Renal from 309 centers in 30 countries, 3,326 had type 1 diabetes and 1,905 had type 2 diabetes—all were normoalbuminuric at baseline. Blood pressure at baseline was within the normal range for the participants with type 1 diabetes and was well controlled in 62 % of the participants with type 2 diabetes who were treated for hypertension. Participants were randomized to receive either candesartan, 16 mg/day increasing to 32 mg/day after one month, or placebo and were followed for at least four years. The urinary albumin excretion rate was measured in two overnight collections at baseline and annually thereafter. In the DIRECT-Renal Program, elevated urinary albumin excretion was defined by a level ≥20 μg/min. If the albumin excretion rate in either sample was ≥20 μg/min, the participant was asked to submit two more overnight collections and if three or more of these collections met this threshold, the participant was considered to have elevated urinary albumin excretion and was counted as a case.

Corresponding author: Dr. Robert G. Nelson, National Institutes of Health, 1550 East Indian School Road, Phoenix, AZ 85014-4972 USA. rgnelson@mail.nih.gov Telephone: (602) 200-5205 Fax: (602) 200-5225.

Financial Disclosure: Dr. Tuttle has received consulting fees regarding diabetes and kidney disease from Eli Lilly and Company and from FibroGen, Inc. She has received an unrestricted research grant from AstraZeneca for a study of DKD.

During a median follow-up of 4.7 years, the pooled hazard ratio for elevated albuminuria in the candesartan group was 0.95 times (95 % CI, 0.78–1.16; p=0.60) that of the placebo group, reflecting a non-significant 5 % decline in the incidence of elevated urinary albumin excretion in the pooled group treated with candesartan relative to the group receiving placebo. The hazard ratios for the individual studies did not differ substantially from the pooled analysis. Similarly, although treatment with candesartan did significantly reduce the annual rate of change of urinary albumin excretion relative to placebo, the change was only 5.5 % lower (95 % CI, 0.7–10.1 %; p=0.024) and was not considered clinically relevant.

The DIRECT-Renal investigators concluded that candesartan had no effect on the primary prevention of elevated urinary albumin excretion over 4.7 years in normoalbuminuric and normotensive patients with type 1 diabetes or in normoalbuminuric patients with type 2 diabetes who were either normotensive or hypertensive. They suggested that the lack of efficacy of candesartan in the DIRECT-Renal participants might be due, in part, to the low prevalence of vascular disease in this relatively young cohort (mean age of participants was 30–35 years in the type 1 studies and 57 years in the type 2 study; pooled mean age was 40 years). Previous studies of primary prevention involving older participants with type 2 diabetes, higher blood pressure, and substantially greater risk for cardiovascular disease did report salutary effects of renin-angiotensin system (RAS) blockade on primary prevention of elevated urinary albumin excretion [4–6].

Renin-Angiotensin System Study (RASS)

RASS was a 5-year randomized double-blinded placebo-controlled clinical trial that enrolled 285 normotensive patients with type 1 diabetes and normal urinary albumin excretion from three centers in three countries [3]. The trial was designed to assess whether the ACE inhibitor enalapril or the ARB losartan would slow the development and progression of kidney disease relative to placebo. Participants were randomized to receive either 10 mg of enalapril daily, 50 mg of losartan daily, or a placebo. Due to emerging data that indicated greater reduction in proteinuria with higher doses of renin angiotensin system inhibitors, the amounts of study drug administered were increased midway through RASS so that participants received double the initial doses for the last 3 years. This trial is unique in that the pre-specified primary study endpoint was a change in the fraction of glomerular volume occupied by mesangium, a robust structural endpoint providing unequivocal evidence of kidney disease progression. Secondary renal endpoints included changes in other glomerular, vascular, tubular, and interstitial morphometric variables, changes in the glomerular filtration rate (GFR) assessed by plasma disappearance of iohexol, and changes in albuminuria. Percutaneous kidney biopsies were performed just prior to randomization and after five years of treatment.

Of the 285 participants enrolled in the study, 90 % completed both kidney biopsies. The change in mesangial fractional volume associated with placebo was not significantly different from that with either enalapril (p=0.16) or losartan (p=0.17). In addition, no differences between groups were found for any other measured morphometric variables. GFR declined equivalently in all three groups. Of note, the albumin excretion rate increased significantly from baseline only in the participants who received losartan (p=0.04), and the 5-year cumulative incidence of microalbuminuria (defined in RASS as 20–200 μg/min) was 17 % in this group, compared with 6 % in the placebo group and 4 % in the enalapril group. The RASS investigators concluded that there were no structural or functional benefits to the kidney from blockade of the RAS with either an ACE inhibitor or an ARB in normotensive patients with type 1 diabetes and normoalbuminuria.

Taken together, these trials resoundingly refute the widely-held belief that RAS blockade is beneficial in DKD prevention or management at all stages. Indeed, the available evidence even suggests potential for harm from an ARB in the primary prevention setting [3].

HOW DO THESE STUDIES COMPARE TO PRIOR STUDIES?

As noted above, the previously reported beneficial effect of RAS blockade on primary prevention of elevated albuminuria in some older patients with type 2 diabetes [4–6] may reflect increased vascular RAS activity associated with hypertension and cardiovascular disease [2]. The current studies indicate that this benefit does not extend to those without these conditions. EUCLID (EURODIAB controlled trial of lisinopril in insulin dependent diabetes) [7] also reported a reduced incidence of elevated albuminuria in normotensive patients with type 1 diabetes, although the effect was not statistically significant, and therefore, this study's results should be considered inconclusive. Although RAS blockade may reduce the frequency of progression to microalbuminuria in some patients with diabetes, the long-term efficacy of such a reduction is questionable, given the lack of preservation of kidney structure or function in RASS participants who received these medicines.

The apparent lack of value of RAS blockade in many patients with either type 1 or type 2 diabetes who do not have elevated blood pressure or urinary albumin excretion indicates that management of these patients to prevent the development of DKD requires other approaches. At present, intensive glycemic control has the strongest evidence base for DKD prevention. This evidence was first established in type 1 diabetes by the Diabetes Control and Complications Trial (DCCT) [8] followed by its long-term observational follow-up study, DCCT- Epidemiology of Diabetes Interventions and Complications (EDIC) [9]. Subsequent studies in type 2 diabetes, the largest and most notable of which was the United Kingdom Prospective Diabetes Study (UKPDS), produced similar findings of reduced risk of DKD with intensive glycemic control [10–13].

However, a note of caution is in order with regard to *overly* intensive glycemic control in patients with long-standing type 2 diabetes. Three recent clinical trials that sought to reduce the target hemoglobin A1c (HbA1c) to levels below <7 % (i.e., HbA1c <6–6.5 %), found no benefit on cardiovascular outcomes and one, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, found higher death and cardiovascular event rates with more aggressive attempts to normalize blood glucose [14–16]. Although a companion trial, ADVANCE (Action in Diabetes and Cardiovascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) found a reduced risk of new onset DKD with a very low HbA1c goal, no cardiovascular benefits emerged [15]. Safety concerns are also paramount–each of the three recent trials showed a dramatic increased risk of severe hypoglycemia in the groups with the lower HbA1c goals. As such, the primary ACCORD results along with the increased risk of hypoglycemia raise a red flag about attempts to "normalize" glycemia in this population. Even if long-term cardiovascular and survival benefits should emerge, there may be a grave up-front cost of overly intensive glycemic control for these high-risk patients. Taken together, the current evidence does not support lowering the HbA1c goal beyond <7 %, except possibly for younger patients with new-onset diabetes who do not have complications, co-morbidities, or recurrent and severe hypoglycemia.

Clearly, the most effective strategy to prevent DKD is prevention of diabetes! The DPP (Diabetes Prevention Program) convincingly showed the remarkable benefit of lifestyle modification by diet, weight loss, and exercise [17]. From a public health standpoint,

prevention of DKD and other major diabetic complications will be most effectively addressed by preventing diabetes itself.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

Approximately 30 % of type 1 diabetic patients and 40 % of those with type 2 diabetes develop DKD [1]. Despite the wide availability of “effective” therapies, diabetes remains the most common cause of kidney failure with more than half (54 %) of incident cases of treated kidney failure attributable to DKD in the United States at the last report [18]. Moreover, kidney failure is more common in older people and non-white populations. Perhaps most sobering is a high death rate, dominated by cardiovascular causes, of approximately 20 % per year among those with DKD once they develop macroalbuminuria or reduced kidney function [19, 20].

The introduction of new and promising treatments for a disease that has such a grim prognosis is inevitably a source of optimism for clinicians and researchers alike. A risk of such optimism is that assumptions about the efficacy of the treatment in various situations are made before sufficient evidence is available. Accordingly, the decision by the Work Group that prepared the KDOQI™ Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease [1] to require strong evidentiary basis for each of the clinical practice guidelines was correct. Notably, no recommendation was made about the use of ACE inhibitors or ARB for primary prevention of DKD. At the time the guidelines were published, this view was strongly challenged by some who believed, despite the lack of evidence, that use of ACE inhibitors and/or ARB for DKD prevention or treatment across various stages was self-evident based on extrapolation from studies of treating hypertensive diabetic patients with overt nephropathy and experimental models. The findings from the studies under discussion demonstrate the importance of adhering to a strict interpretation of the evidence when formulating guidelines intended to propose the best possible care within the context of presently available medical knowledge. This approach was rigorously adhered to by the Work Group that prepared the guidelines. It is also important to disclose that the first authors of the papers discussed in this editorial were members of this Work Group. Additionally, both the Joint National Committee and the American Diabetes Association recommend treatment of hypertensive diabetic patients with ACE inhibitors or ARB, but these recommendations are based primarily on cardiovascular risk reduction rather than prevention of DKD [21, 22]. By contrast, the KDOQI™ Clinical Practice Guidelines on Hypertension and Anti-Hypertensive Agents in Chronic Kidney Disease recommend ACE inhibitors or ARB in patients with diabetic kidney disease based on their efficacy in slowing kidney disease progression [23]. The KDOQI™ Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease [1] appropriately note that the evidence base for this recommendation is much stronger for patients with macroalbuminuria than microalbuminuria.

Results from the recent studies discussed above illustrate the need for better biomarkers of early DKD. Classification of CKD stages currently uses definitions of disease severity that lump patients with similar phenotypes together despite potentially different mechanisms that are inconsistently associated with progression of morphologic lesions. Further investigation into relevant molecular pathways may lead to stage-specific molecular fingerprints that can be easily identified in blood or urine. Identification of these specific metabolic pathways may form the basis of a personalized approach to CKD management employing treatment strategies that interrupt disease mechanisms operative in the individual patient, in contrast to our current clinical phenotype-based management. We are entering an era of discovery for which the science of genomics, proteomics, transcriptomics, and metabalomics holds great

promise that will hopefully lead to validated approaches to better characterizing patients. In the meantime, prevention and treatment of DKD across stages should be based on the best available clinical evidence.

Acknowledgments

Support: Dr. Nelson is supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases.

References

1. National Kidney Foundation. KDOQI™ Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Dis. 2007; 49:S1–S180.
2. Bilous R, Chaturvedi N, Sjølie AK, Fuller J, Klein R, Orchard T, et al. Effect of Candesartan on Microalbuminuria and Albumin Excretion Rate in Diabetes: three randomized trials. Ann Intern Med. 2009; 151:11–20. [PubMed: 19451554]
3. Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T, et al. Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes. N Engl J Med. 2009; 361:40–51. [PubMed: 19571282]
4. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, et al. Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators: Preventing microalbuminuria in type 2 diabetes. N Engl J Med. 2004; 351:1441–1451.
5. Patel A. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomized controlled trial. Lancet. 2007; 370:829–840. [PubMed: 17765963]
6. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2003; 342:145–153.
7. The EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. Lancet. 1997; 349:1787–1792. [PubMed: 9269212]
8. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329:977–986. [PubMed: 8366922]
9. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med. 2000; 342:981–989. [PubMed: 10744502]
10. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352:837–853. [PubMed: 9742976]
11. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998; 352:854–865. [PubMed: 9742977]
12. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995; 28:103–117. [PubMed: 7587918]
13. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359:1577–1589. [PubMed: 18784090]
14. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358:2545–2559. [PubMed: 18539917]

15. The Action in Diabetes and Cardiovascular Disease. Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) Collaborative Group: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008; 358:2560–2572. [PubMed: 18539916]

16. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009; 360:129–139. [PubMed: 19092145]

17. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346:393–403. [PubMed: 11832527]

18. U.S. Renal Data System. Atlas of End-Stage Renal Disease in the United States. Vol. 2. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 2009. USRDS 2009 Annual Data Report.

19. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003; 63:225–232. [PubMed: 12472787]

20. U.S. Renal Data System. Atlas of Chronic Kidney Disease in the United States. Vol. 1. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 2009. USRDS 2009 Annual Data Report.

21. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003; 42:1206–1252. [PubMed: 14656957]

22. American Diabetes Association. Clinical Practice Recommendations 2009. Diabetes Care. 2009; 31:S1–S98.

23. National Kidney Foundation. KDOQI™ Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Am J Kidney Dis. 2004; 43:S1–S290. [PubMed: 15114537]