How High Should an ACE Inhibitor or Angiotensin Receptor Blocker Be Dosed in Patients with Diabetic Nephropathy?

*Marc S. Weinberg, MD, Nicholas Kaperonis, MD, and George L. Bakris, MD**

Address
*Hypertension Clinical Research Center, Rush-Presbyterian-St. Luke's Medical Center, 1700 W. Van Buren, Suite 470, Chicago, IL 60612, USA.
E-mail: george_l_bakris@rsh.net

Current Hypertension Reports 2003, **5:**418–425
Current Science Inc. ISSN 1522-6417

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), two drug classes that effectively block the actions of the renin-angiotensin system (RAS), have unique capabilities as antihypertensive agents. Recent landmark clinical trials have demonstrated their important roles as primary therapy for the prevention of renal disease in diabetes. The optimal dosage of these RAS blockers required to slow the progression of renal disease or impair the development of cardiovascular risk is not known. However, data from many studies strongly support the use of the higher doses of ACE inhibitors or ARBs to reduce proteinuria. All studies of kidney disease progression demonstrate benefit on slowing only when blood pressure is reduced when using higher doses. In order to accrue the optimum benefit from ACE inhibitors and ARBs, the dose-response relationship for diabetic renal disease will have to be determined. The best strategy, *ie*, supramaximal doses of ACE inhibitors or ARBs or combining them, is still a matter of debate but may be resolved soon by results of ongoing studies.

Introduction

Diabetic nephropathy is the leading cause of end-stage renal disease in the United States [1]. Clinical practice guidelines recommend angiotensin-converting enzyme (ACE) inhibitors in both hypertensive and normotensive type 1 diabetic patients with microalbuminuria or overt nephropathy [2]. More recently, four major renal outcome studies have provided evidence compelling the American Diabetes Association to recommend angiotensin receptor blockers (ARBs) as the treatment of choice in type 2 diabetes with diabetic nephropathy and ARBs or ACE inhibitors in patients with microalbuminuria [3,4•,5•,6,7•].

Proteinuria is well established as a marker and independent risk factor for the development of cardiovascular (CV) and renal diseases [8]. A recent study reported that the use of an ACE inhibitor to reduce proteinuria resulted in improved renal and CV outcomes [6]. Titrating the dose of ACE inhibitors or ARBs to maximally reduce proteinuria is a strategy that has been advocated but has not yet been tested in a study to determine renal and CV outcomes [9–12]. The doses of ARBs and ACE inhibitors to effectively block the renin-angiotensin system (RAS) have been determined by blood pressure (BP) reduction rather than by effecting renal and/or CV outcomes.

Studies have demonstrated the importance of using higher doses of ACE inhibitors and/or ARBs, beyond BP lowering, for greater reductions in proteinuria [12,13]. Blockade of both the circulating and tissue RAS to reduce systemic and renal hemodynamics and intrarenal effects of angiotensin II are the primary renoprotective actions of ACE inhibitors and ARBs. Consideration of dose and length of therapy is of prime importance [12–15].

The purpose of this review is to examine those dose comparative studies in diabetic subjects that have evaluated the effect of usual or high doses of RAS blockers as monotherapy or as combination (ARBs and/or ACE inhibitors) therapy in order to achieve maximal blockade of the RAS. In addition, by examining studies based on dose-related titrations of ACE inhibitors and ARBs, emphasis will be placed on determining "how high is high" by the magnitude of the reduction in proteinuria.

Importance of Dosing

Benefits of RAS blockade in preventing the progression of diabetic renal disease have largely been attributed to reductions in BP and renal hemodynamic changes. Recent studies have demonstrated that ACE inhibitors and ARBs reduce proteinuria to a greater extent when matched for BP against other non-RAS antihypertensive agents [16]. These BP-independent effects of RAS blockade may be due to inhibition of the intrarenal or local RAS that is active in diabetes [17]. Reducing the effects of angiotensin II in the glomerulus may act to improve glomerular permselectivity, a process that may be partially independent from changes in glomerular pressure [18].

The existence and function of a local or intrarenal RAS is well established and may require higher doses of ACE inhibitors or ARBs for effective tissue RAS inhibition, despite effective systemic RAS blockade [11]. Incomplete blockade of the intrarenal RAS may be due to ACE escape and to the existence of other non-ACE enzymes, such as chymase, that can convert angiotensin I to its active form [19,20]. The presence of non-ACE pathways for the generation of intrarenal angiotensin II may be responsible for the progression of renal disease in some patients with diabetes despite chronic ACE inhibitor therapy [21].

Strategies that result in more complete blockade of the RAS may lead to better long-term outcomes in reducing the progression of renal disease. The difficulty in utilizing one of the various strategies to enhance RAS blockade is the lack of evidence to determine what approach is optimal. Sodium restriction or concomitant diuretic administration will lead to a heightened RAS activity, thus allowing blockade of the RAS to result in greater reductions in proteinuria [22]. Dosing ACE inhibitors or ARBs twice a day, increasing the dose of monotherapy, or combining ACE inhibitors and ARBs will also result in greater increases in plasma renin activity and therefore a more complete RAS blockade [14,20,23]. Dosing ACE inhibitors or ARBs beyond BP lowering (supramaximal doses) has also shown greater RAS blockade, but it may not be as effective as combined ACE inhibitors plus ARB therapy [10,24,25]. The difficulty in choosing to use ACE inhibitors and/or ARBs at higher doses has been a direct consequence of the paucity of clinical data to guide therapy. Almost all studies examining the benefit of ACE inhibitors or ARBs in renal disease have used moderate doses that are typically associated with their BP-lowering effects [9].

Current clinical evidence suggests that using doses of ACE inhibitors or ARBs higher than is typically being used have reported greater reductions in proteinuria [11,12]. The importance of using higher doses of drug to block the RAS has also been confirmed by studies that have found additional reductions in proteinuria when an ARB has been given to patients already on maximal ACE inhibitors therapy [23,26••]. Preliminary clinical evidence would support the use of higher doses or combined therapy as important strategies to enhance RAS blockade and thereby lead to better renal and CV outcomes.

Nonrenal and Cardiovascular Dose-response Studies

Recent CV outcome trials using ARBs have suggested that higher doses may confer greater benefit through more complete blockade of the RAS. Recently, OPTIMAAL and ELITE II reported losartan 50 mg/d was not as effective as captopril 150 mg/d in preventing the CV events associated with postmyocardial infarction and/or chronic heart failure (CHF), respectively [27,28]. However, the dose of losartan may not have been comparable to the dose of captopril, and thus losartan may not have been adequate in completely blocking the RAS. In contrast to OPTIMAAL and ELITE II, LIFE and RENAAL using up to 100 mg of losartan demonstrated effective reductions in CV events and progressive renal failure [5•,29,30]. These conflicting results between trials suggest that dose may play a very important role in the BP-independent tissue protective effects of ARBs and ACE inhibitors.

However, in other studies with ACE inhibitors and/or ARBs there have been mixed results in the evaluation of higher doses. In CHF studies, the benefits of using higher doses of ACE inhibitors or ARBs have been moderate [31–36] to neutral [37–40]. In the Val-HeFT study, there was no benefit on CV mortality when an ARB was added to standard therapy in CHF, which included an ACE inhibitor and β-blocker [32]. It is well known that ACE inhibitors and β-blockers both affect the RAS with the net result being very low plasma angiotensin II levels when used together, thereby obviating the need for additional ARB therapy in patients well controlled on standard therapy in CHF (ACE inhibitor plus β-blocker plus diuretic) [41].

In other CV disease states, a substudy of the HOPE trial, a prospective, randomized, clinical trial in patients with hypertension, diabetes, and left ventricular hypertrophy, evaluated two doses of the ACE inhibitor ramipril, 2.5 mg/d and 10 mg/d [42]. The study compared ACE inhibitor therapy with placebo for the development of atherogenesis in the carotid circulation. Even though the study was not powered to perform comparisons among the two ramipril doses (2.5 vs 10 mg/d), the high-dose group demonstrated a slower rate of progression of carotid atherosclerosis.

Based on the available data, higher doses of RAS blockers do not appear to confer additional benefits in patients being treated with standard therapy in CHF and post–myocardial infarction. However, higher doses of ACE inhibitors and/or ARBs play an important role in diabetes and renal disease by ensuring a more complete blockade of the intrarenal RAS. A recent meta-analysis of renoprotection studies in patients with nondiabetic renal disease demonstrated a linear dose-response relationship, *ie*, higher doses were associated with better renal outcomes [43].

Despite the proven benefits of ACE inhibitor or ARB therapy in patients with diabetic nephropathy, a large number of patients still developed worsening renal outcomes [4•,5•,44]. Although increasing the dose of the ACE inhibitor or ARB or combining the two therapies may bring more benefit, there are still other important factors to control (aggressive BP lowering, dietary sodium intake, glucose control, protein consumption, use of statins, and so forth) to help limit the progression of CV and renal disease.

Type 1 Diabetes and Renal Disease

The importance of antagonizing the action of angiotensin II in diabetes is well established to reduce proteinuria and preserve renal function [6,30,45]. However, there is a need to

Table 1. Studies in type I diabetics with microalbuminuria and nephropathy (macroalbuminuria ± renal insufficiency)

Study	Drug, daily dose	Change in AER, %	Change in MAP, %	Change in GFR, %
Microalbuminuria				
O'Hare *et al.* [46]	Placebo	+29.6	+3*	NS
	Ramipril 1.25 mg	-26.5	-4	NS
	Ramipril 5 mg	-15.5	-3	NS
Macroalbuminuria				
Okada *et al* [47]	ACE inhibitor + ARB	-28	-9	NA
Andersen *et al.* [48•]	Enalapril 10 mg	-45	-6	-1
	Losartan 20 mg	-59	-11	-3
	Losartan 50 mg	-33	-9	1
	Losartan 100 mg	-44	-8	-1
Andersen *et al.* [49•]	Losartan 50 mg	-30	-5	-2
	Losartan 100 mg	-48	-8	-4
	Losartan 150 mg	-44	-6	-4
Laverman *et al.* [50]	Losartan 50 mg	-34	-8†	NS
	Losartan 100 mg	-45	-13	NS
	Losartan 150 mg	-47	-11	NS
Jacobsen *et al.* [51]	Benazepril 20 mg	-65	-6	-4
	Valsartan 80 mg	-65	-6	-5
	Benazepril 20 mg + valsartan 80 mg	-80	-20	-12
Jacobsen *et al.* [26••]	Enalapril 40 mg + irbesartan 300 mg	-25	-6	-3

*Systolic blood pressure only given.
†MAP responses are reported in responders.
ACE—angiotensin-converting enzyme; AER—albumin excretion rate, ARB—angiotensin receptor blocker; GFR—glomerular filtration rate; MAP—mean arterial pressure; NA—not available; NS—not studied.

determine the optimal strategy in order to maximize blockade of the RAS. We reviewed seven studies in type I diabetic patients with micro- or macroalbuminuria that evaluated different doses of monotherapy using ACE inhibitors or ARBs or utilized combination (ARBs plus ACE inhibitors) therapy (Table 1) [26••,46,47,48•,49•,50,51].

Microalbuminuria

Several clinical studies in normotensive and hypertensive patients with type I diabetes have demonstrated reduction of microalbuminuria with usual doses of ACE inhibitors, independent of BP reduction [52]. Trials evaluating the importance of dose in microalbuminuric patients with type I diabetes have been positive but few in number (Table 1). A study by O'Hare *et al.* [46] evaluated low versus usual doses of ramipril (1.25 mg/d vs 5 mg/d) in the progression of microalbuminuria in type I normotensive diabetics. Urinary albumin excretion rates were lower in the two ramipril groups versus placebo but not significantly different from each other.

The second study by Bakris *et al.* [13] evaluated supramaximal doses of lisinopril in 15 normotensive subjects with insulin-dependent diabetes mellitus (IDDM) in order to determine its effect on microalbuminuria. Dosage of lisinopril was titrated over 3 months from 20 to 100 mg/d, followed by the supramaximal dose for the next 15 months. Evaluation at 6, 12, and 18 months demonstrated that the lisinopril group had a progressive reduction in microalbuminuria by 48%, 62%, and 75%, respectively (Fig. 1). There was an 8 mm Hg reduction in mean arterial pressure (MAP) at 3 months, with no change in MAP during the 3- to 18-month study period. This study was the first to demonstrate the importance of dose (higher ACE inhibitor doses than those used for BP lowering) and time in order to achieve maximal protein lowering effects.

Macroalbuminuria

Two combination ACE inhibitor and ARB therapy trials, as well as three comparative trials of multiple doses of monotherapy, have been investigated in type I diabetics with overt nephropathy (Table 1). The landmark study by Lewis *et al.* [44] first demonstrated the renoprotective effect of ACE inhibitors in preventing the progression of chronic renal failure. So striking were these data that it was the first time that one trial convinced the US Food and Drug Administration (FDA) to change the labeling of a drug, with captopril subsequently being coined "renoprotective." As the beneficiary of this action, the trial compared the effects of conventional therapy with captopril on BP reduction and renal function. Although both groups had similar reductions in BP, captopril led to significant reductions in proteinuria as well as prevented the doubling of serum creatinine. These BP-independent effects of captopril were very intriguing and compelled other investigators to

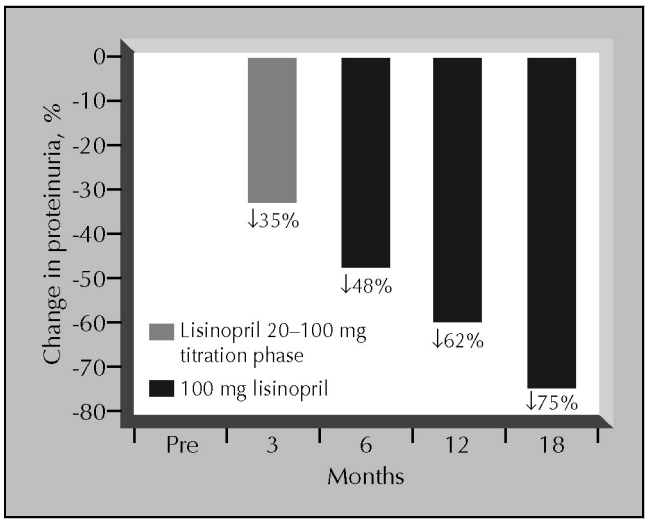

Figure 1. Progressive reductions in microalbuminuria using high-dose angiotensin-converting enzyme inhibitor therapy in normotensive patients with type 1 diabetes. (*Adapted from* Bakris *et al*. [13].)

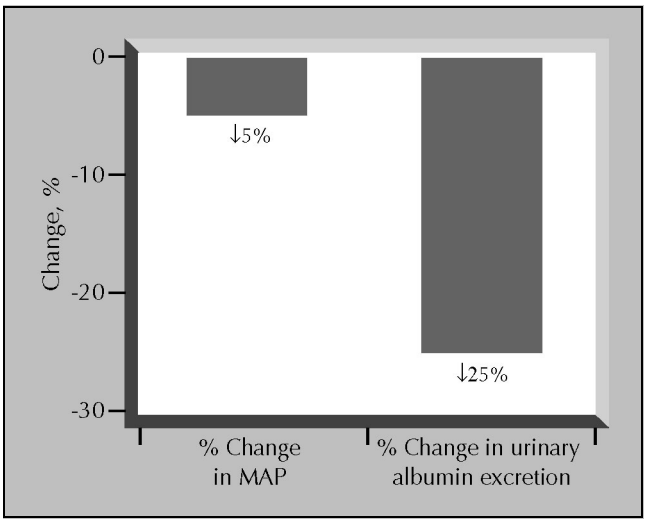

Figure 2. High-dose angiotensin receptor blocker therapy added to maximal recommended dose of angiotensin-converting enzyme inhibition in patients with diabetic nephropathy [26••].

examine the importance of using higher doses of ACE inhibitors or ARBs beyond their ability to lower systemic BP in a series of later studies.

In three dose-response protocols, the optimal dose of losartan in type 1 diabetes with nephropathy was with the highest approved dose of 100 mg/d [48•,49•,50]. Reductions in proteinuria at 100 mg/d (-44% to -48%) were significantly higher than 50 mg/d (-30% to -34%) . However, doses above 100 mg/d resulted in neither a further reduction in albuminuria nor BP [49•,50].

In order to further evaluate combination ACE inhibitors and ARBs versus monotherapy with each class alone, Jacobsen *et al*. [51] administered to diabetics either valsartan (80 mg/d), benazepril (20 mg/d), or the combination of both benazepril (20 mg/d) and valsartan (80 mg/d). Combination therapy led to an additional 43% reduction in albuminuria. Another study by Jacobsen *et al.* [26••] evaluated whether adding high-dose ARB therapy (300 mg/d irbesartan) to patients with diabetic nephropathy on existing high-dose ACE inhibitor therapy (enalapril 40 mg/d) had any additional effects in patients with diabetic nephropathy. After 8 weeks of combination therapy albuminuria was further reduced by 25% compared with ACE inhibitors therapy (Fig. 2). There were no further changes in glomerular filtration rate and plasma potassium levels, while small additional reductions in BP were noted. This study suggests that dual blockade of the RAS is superior to maximally recommended doses of ACE inhibitors with respect to BP and protein lowering.

In another ACE inhibitor plus ARB combination study, changes in urinary protein excretion were increased beyond that seen with monotherapy and was greatly influenced by a subset of subjects on a low Na^+ diet. Subjects on low Na^+ intake had a greater reduction in proteinuria (40% ± 33%) compared with the subjects on a high Na^+ intake (13% ± 40%) [47]. These results suggest that Na^+ intake can greatly affect the response to RAS blockade by activating or inhibiting RAS activity and the benefit of combination therapy is chiefly attributed to a greater ability to antagonize the RAS [53]. Increasing the response to ARB and/or ACE inhibitor therapy even at high doses can then be improved by pretreating with a diuretic or minimizing salt intake [22].

Finally, ACE inhibitors represent the most powerful and indisputable agents for the delay of diabetic nephropathy in patients with type 1 diabetes. However, since recent studies with ACE inhibitors and ARBs in combination suggest probable additional renoprotective effects than using monotherapy alone, further studies need to be performed in order to determine whether supramaximal doses of ACE inhibitors or ARBs alone would provide equal additive benefit. However, it appears that the optimal renoprotective dose of losartan was at its maximally approved level of 100 mg, since going beyond this dose provided no added benefit. It is not known if this result will also be true for other ARBs or is unique to losartan [20].

Type 2 Diabetes and Renal Disease

In patients with type 2 diabetes and microalbuminuria, both ACE inhibitors or ARBs are recommended as standard therapy to reduce proteinuria and preserve renal function (Micro-HOPE, IRMA-2). In patients with type 2 diabetes and nephropathy (macroalbuminuria) based on the outcome results from the RENAAL and IDNT studies, ARBs are recommended as first-line therapy [4•,5•]. We have reviewed four additional comparative dose trials in albuminuric patients with type 2 diabetes where different doses of ACE inhibitors or ARBs were tested and two ACE inhibitors plus ARB combination studies were conducted (Table 2) [7•,54–57,58•].

Table 2. Studies in type 2 diabetics with microalbuminuria and nephropathy (macroalbuminuria ± renal insufficiency)

Study	Drug, daily dose	Change in AER, %	Change in MAP, %	Change in GFR, %
Microalbuminuria				
Mogensen *et al.* [54] (CALM study)	Candesartan 16 mg	-24*	-10	NS
	Lisinopril 20 mg	-39*	-11	-5
	Combination	-50*	-17	-4
Parving *et al.* [7•] (IRMA-2 study)	Placebo	-2	0	-3
	Irbesartan 150 mg	-24	0	-4
	Irbesartan 300 mg	-38	-1	-6
de Pablos-Velasco *et al.* [55]	Losartan 50 mg	-	-7	-
	Losartan 100 mg	-27	-10	7†
	Losartan 50 mg + HCTZ 12.5 mg	-41	-11	0†
Muirhead *et al.* [56]	Placebo	18	0	-8
	Captopril	-26	-2	0
	Valsartan 80 mg	-28	-4	-7
	Valsartan 160 mg	-21	-4	-11
Macroalbuminuria				
Rossing *et al.* [57]	ACE inhibitor + candesartan 8 mg	-25	-5	-7
Rossing *et al.* [58•]	Candesartan 8 mg	-33	6	-7
	Candesartan 16 mg	-59	-6	-7
	Candesartan 32 mg	-52	-8	-7

*This change is for the ratio of urinary albumin to creatinine (mg/mmol).
†Comparisons of serum creatinine between losartan titrated to 100 mg vs 50 mg and losartan 100 mg vs losartan 50 mg + HCTZ.
ACE—angiotensin-converting enzyme; AER—albumin excretion rate; MAP—mean arterial pressure; GFR—glomerular filtration rate.

Microalbuminuria

The IRMA-2 trial evaluated the effect of increasing the dose of irbesartan from moderate (150 mg/d) to high (300 mg/d) levels [7•]. After a 2-year follow-up period, 300 mg/d of irbesartan was associated with a greater reduction in proteinuria than the moderate dose and was associated with little or no differences in BP [7•]. A similar finding was demonstrated in a smaller study using losartan but not with valsartan [55,56]. In the study with valsartan it was reported that 160 mg/d did not reduce proteinuria any further than that of its lower dose (80 mg/d), but it may be attributed to the low baseline levels of albuminuria (85 mg/d) in this trial [56].

In the CALM study, the combination of candesartan (16 mg/d) and lisinopril (20 mg/d) were compared with the individual components [54]. Initiation of dual therapy once again resulted in both additional reductions in albuminuria as well as greater reductions in systolic BP (decreased 6 mm Hg) and diastolic BP (decreased 5 mm Hg) [54].

Macroalbuminuria

A dose titration study in 23 type 2 diabetic patients was conducted by Rossing *et al*. [58•] where each subject received placebo, candesartan 8 mg/d, 16 mg/d, and 32 mg/d in random order. Results demonstrated that the antiproteinuric effects were dose related up to 16 mg/d, whereas going further (32 mg/d) did not result in any additional reductions in proteinuria. In contrast, a recent study in nondiabetic proteinuric (> 2 g/d) patients suggests that titrating the dose of candesartan, up to its highest approved dose (32 mg/d), will lead to additional reductions in proteinuria, and this may be related to additional reductions in BP [59].

Rossing *et al*. [57] evaluated dual blockade of the RAS in a randomized double-blind crossover study. Subjects were given either candesartan 8 mg/d or placebo added to ACE inhibitors therapy in all subjects in addition to usual antihypertensive therapy. The addition of the ARB candesartan 8 mg/d reduced albuminuria by 25% and lowered 24-hour systolic BP by another 10 mm Hg. They concluded that combination ACE inhibitors and ARB therapy was associated with greater blockade of the RAS by reducing albuminuria and BP.

The landmark IRMA-2 study demonstrated dose-dependent reductions in proteinuria that were partially independent of BP reductions, and that the optimal doses used for renal protection may in fact be greater than those currently being used for BP lowering. However, there are no definitive data currently to state whether or not going beyond the standard doses or combining therapies (ACE inhibitor plus ARB) confers greater benefit. Currently, there are ongoing trials where answers to these questions will soon be available. However, in type 2 diabetes, titrating the dose of the ACE inhibitor or ARB to its maximum approved dose was associated with further reductions in proteinuria.

Optimal Renoprotective Dose

Evidence from clinical trials in patients with diabetes found that the maximum approved doses for ARBs should be used in patients with proteinuria [48•,50,58•]. This has also been supported by similar studies in nondiabetic renal disease patients [24,60]. Based on the studies reviewed, it is apparent that greater benefit can be achieved using high doses of ACE inhibitors or ARBs as monotherapy, but no further antiproteinuric response would be obtained using higher doses than those necessary for effective BP control. However, this is in conflict with another study that demonstrated that supramaximal doses of candesartan resulted in dose-dependent reductions in proteinuria at levels three times the maximal approved dose [11]. Whether or not ARBs, beyond their approved maximum doses, confer a benefit in renal disease is currently being addressed by two trials in patients with type II diabetes. The DROP trial (dosing valsartan up to 640 mg/d) and SMART study (dosing candesartan cilexitil up to 128 mg/d) will further explore the optimal therapeutic effect of ARB therapy in reducing proteinuria [61,62].

What are the options in patients where despite high-dose monotherapy proteinuria is still elevated? An alternative and appropriate strategy, based on limited data, is the combined use of ACE inhibitors and ARBs [52]. The difficulty in determining the effectiveness of this approach has been the tendency to combine very low or moderate doses of ACE inhibitors and ARBs together without first titrating the initial agent to its maximum [47,51,57]. Thus, comparison of trials using low or moderate doses can be complicated to interpret, as well as to compare. However, in a recent study (Fig. 2) when the ARB was added to the maximum dose of the ACE inhibitor, an additional reduction in albuminuria in type I diabetic nephropathy patients occurred [58•]. This has been supported by two recent combination studies in patients with nondiabetic renal disease [13,23]. In the study by Laverman *et al.* [23] where they examined dual therapy, the optimal ACE inhibitor and ARB antiproteinuric dose was initially determined for each patient. After titrating to the patients optimal ACE inhibitor and ARB dose, combined therapy resulted in an additional 29% reduction in proteinuria over that achieved for ACE inhibitor monotherapy. It appears that the benefits of dual therapy are dose dependent, and reflect further inhibition of the intrarenal RAS.

Concern has been raised about using high or supramaximal doses of ACE inhibitors or ARBs, and its consequent negative effects on worsening renal function and greater incidence of hyperkalemia. In the studies reviewed, higher doses of ACE inhibitors and/or ARBs were typically associated with small increases in plasma potassium (0–0.3 mmol/L), no changes in plasma creatinine, and a transient hypotensive effect in some patients [26••,48•, 49•,51,57]. The safety and efficacy of the ARB, candesartan cilexetil, at five times its therapeutic maximum (160 mg/d) was recently tested in 12 hypertensive subjects (seven diabetics) with proteinuria [63]. No adverse effects were reported in that study with no significant changes in plasma potassium and creatinine. Given that ARBs have no dose-limiting side effects, and to a lesser extent ACE inhibitors, it will be possible to safely titrate patients using supramaximal doses of these drugs to determine optimal renoprotective effects [63].

The whole "dosing strategy" issue is characterized by inherent difficulties primarily due to large individual variability in response to RAS blockade therapy. In an attempt to further antagonize the intrarenal (tissue) RAS for renoprotection, higher doses of ACE inhibitors or ARBs or combined therapy have been used along with Na^+ restriction or diuretic administration [53]. However, it is difficult to know the most effective strategy to choose in order to maximize the reduction in proteinuria. To this end, much individual testing is necessary. Searching for the upper limit of dose for total renal protection with ACE inhibitors and/or ARBs should require evaluating the different dose-response curves for each drug alone as monotherapy. Studies addressing this particular question are scarce but are needed to help guide therapeutic decisions [23]. Thus, the optimal dose and strategy for renoprotection using ACE inhibitors and ARBs should be guided by titrating to the maximum antiproteinuric effect [8,9].

Conclusions

ACE inhibitors and ARBs, as monotherapy or in combination, have evolved as accepted first-line agents for delaying the progression of diabetic nephropathy. Currently, recommendations favor ACE inhibitors for type 1 and ARBs or ACE inhibitors for type 2 diabetes as a result of large, controlled clinical trials. Therapeutic goals should be addressed not only for BP reduction, but in diminishing albuminuria as well. In subjects with microalbuminuria, the dose of ARBs or ACE inhibitors should be titrated by the clinician until normoalbuminuria is induced, even if supramaximal doses or a combination of ARBs and ACE inhibitors are necessary. There is evidence that achieving reduction in both microalbuminuria and in heavy proteinuria at greater doses than those used to control BP may be required using monotherapy or a combination of these RAS blockers. Nevertheless, the question of how high the doses of ACE inhibitors or ARBs must be for optimal benefit in diabetic nephropathy has not been widely answered. Screening should be performed on all subjects with risk factors for microalbuminuria (hypertension, hyperlipidemia, diabetes, coronary artery disease, smoking, positive family history, CV disease, obesity, chronic renal disease, and trace or 1+ proteinuria on urinalysis), and therapy should be initiated to normalize or reduce proteinuria in either normotensive or hypertensive subjects. The studies completed thus far have helped to raise the question, "How high is high?" In order to address how high the doses of ACE inhibitors and ARBs must be for maximal tissue blockade of the RAS, long-term

renal and CV outcome studies need to be performed using the most effective antihypertensive and antiproteinuric dose.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. **K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative.** *Am J Kidney Dis* 2002, **39:**S1–S246.
2. Arauz-Pacheco C, Parrott MA, Raskin P: **Treatment of hypertension in adults with diabetes.** *Diabetes Care* 2003, **26:**S80–S82.
3. Molitch ME, DeFronzo RA, Franz MJ, *et al.*: **Diabetic nephropathy.** *Diabetes Care* 2003, **26:**S94–S98.
4. • 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 Engl J Med* 2001, **345:**851–886.

The first of the two large studies that accounted for an ARB recommendation in type 2 diabetes. In this study the superiority of irbesartan was shown compared with amlodipine.

5. • 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:**861–869.

This study clearly disclosed the significant effect of the ARB (losartan) on preventing the progression to hard endpoints.

6. Heart Outcomes Prevention Evaluation (HOPE) Investigators: **Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy.** *Lancet* 2000, **355:**253–259.
7. • 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:**870–878.

This study included two different doses of irbesartan for treatment of type 2 diabetics with proteinuria. The higher dose (300 mg) was more powerful toward favorable changes of proteinuric status.

8. Miettinen H, Haffner SM, Lehto S, *et al.*: **Proteinuria predicts stroke and other atherosclerotic vascular disease events in nondiabetic and non-insulin-dependent diabetic subjects.** *Stroke* 1996, **27:**2033–2039.
9. Navis G, de Zeeuw D: **Titrating for antiproteinuric effect: the clue to renoprotection?.** *J Hum Hypertens* 1996, **10:**669–673.
10. De Jong PE, Navis G, de Zeeuw D: **Renoprotective therapy: titration against urinary protein excretion.** *Lancet* 1999, **354:**352–353.
11. Peters H, Ritz E: **Dosing angiotensin II blockers—beyond blood pressure.** *Nephrol Dial Transplant* 1999, **14:**2568–2570.
12. Weinberg MS, Cord R, Weinberg AJ, Zappe DH: **The effect of high dose angiotensin II receptor blockade beyond maximal recommended doses in reducing urinary protein excretion.** *J Renin Angiotensin Aldosterone Syst* 2001, **2:**S196–S198.
13. Bakris GL, Slataper R, Vicknair N, Sadler R: **ACE inhibitor mediated reductions in renal size and microalbuminuria in normotensive, diabetic subjects.** *J Diabetes Complications* 1994, **8:**2–6.
14. Nakao N, Yoshimura A, Morita H, *et al.*: **Combination treatment of angiotensin II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomized controlled trial.** *Lancet* 2003, **361:**117–124.
15. Forclaz A, Maillard M, Nussberger J, *et al.*: **Angiotensin II receptor blockade. Is there truly a benefit of adding an ACE Inhibitor?** *Hypertension* 2003, **41:**31–36.
16. Viberti G, Wheeldon NM: **Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect.** *Circulation* 2002, **106:**672–678.
17. Price DA, Porter LE, Gordon M, *et al.*: **The paradox of the low-renin state in diabetic nephropathy.** *J Am Soc Nephrol* 1999, **10:**2382–2391.
18. Ruggenenti P, Remuzzi G: **The renoprotective action of angiotensin-converting enzyme inhibitors in diabetes.** *Exp Nephrol* 1996, **4:**53–60.
19. Hollenberg NK: **AT(1)-receptor blockade and the kidney: importance of non-ACE pathways in health and disease.** *J Hum Hypertens* 2002, **16:**S59–S63.
20. Weinberg MS, Weinberg AJ, Zappe DH: **Effectively targetting the renin-angiotensin-aldosterone system in cardiovascular and renal disease: rationale for using angiotensin II receptor blockers in combination with angiotensin-converting enzyme inhibitors.** *J Renin Angiotensin Aldosterone Syst* 2000, **1:**217–233.
21. Shiigai T, Shichiri M: **Late escape from the antiproteinuric effect of ace inhibitors in nondiabetic renal disease.** *Am J Kidney Dis* 2001, **37:**477–483.
22. Buter H, Hemmelder MH, Navis G, *et al.*: **The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide.** *Nephrol Dial Transplant* 1998, **13:**1682–1685.
23. Laverman GD, Navis G, Henning RH, *et al.*: **Dual renin-angiotensin system blockade at optimal doses for proteinuria.** *Kidney Int* 2002, **62:**1020–1025.
24. Haas M, Leko-Hohr Z, Erler C, Mayer G: **Antiproteinuric versus antihypertensive effects of high-dose ACE inhibitor therapy.** *Am J Kidney Dis* 2002, **40:**458–463.
25. Komine N, Khang S, Wead LM, *et al.*: **Effect of combining an ACE inhibitor and an angiotensin II receptor blocker on plasma and kidney tissue angiotensin II levels.** *Am J Kidney Dis* 2002, **39:**159–164.
26. •• Jacobsen P, Andersen S, Rossing K, *et al.*: **Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy.** *Kidney Int* 2003, **63:**1874–1880.

This study evaluated the antiproteinuric effects of adding high-dose ARB therapy (irbesartan 300 mg/d) to pre-existing maximal ACE inhibitor therapy.

27. Kickstein K, Kjekshus J, and the OPTIMAAL Steering Committee for the OPTIMAAL Study Group: **Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infacrction: the OPTIMAAL randomized trial.** *Lancet* 2002, **360:**752–760.
28. Pitt B, Poole-Wilson PA, Segal R, *et al.*: **Effect of losartan compated with captopril on mortality in patients with symptomatic heart failure: randomized trial-the Losartan Heart Failure Survival Study ELITE II.** *Lancet* 2000, **355:**1582–1587.
29. Dahlof B, Devereux RB, Kjeldsen SE, *et al.*: **Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study(LIFE): a randomized trial against atenolol.** *Lancet* 2002, **359:**995–1003.
30. Lindholm LH, Ibsen H, Dahlof B, *et al.*, for the LIFE study group: **Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol.** *Lancet* 2002, **359:**1004–1010.
31. Packer M, Poole-Wilson PA, Armstrong PW: **Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group.** *Circulation* 1999, **100:**2312–2318.
32. van Veldhuisen DJ, Genth-Zotz S, Brouwer J, *et al.*: **High- versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril.** *J Am Coll Cardiol* 1998, **32:**1811–1818.

33. Cohn JN, Tognoni G, for the VALSARTAN Heart Failure Trial Investigators: **A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure.** *N Engl J Med* 2001, **345:**1667–1675.
34. Pacher R, Stanek B, Globits S, *et al.*: **Effects of two different enalapril dosages on clinical, haemodynamic and neurohumoral response of patients with severe congestive heart failure.** *Eur Heart J* 1996, **17:**1223–1232.
35. Clement DL, De Buyzere M, Tomas M, Vanavermaete G: **Long-term effects of clinical outcome with low and high dose in the Captopril in Heart Insufficient Patients Study (CHIPS).** *Acta Cardiol* 2000, **55:**1–7.
36. Luzier AB, Forrest A, Adelman M, *et al.*: **Impact of angiotensin-converting enzyme inhibitor underdosing on rehospitalization rates in congestive heart failure.** *Am J Cardiol* 1998, **82:**465–469.
37. NETWORK Investigators: **Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison.** *Eur Heart J* 1998, **19:**481–489.
38. Nanas JN, Alexopoulos G, Anastasiou-Nana MI, *et al.*: **Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. High Enalapril Dose Study Group.** *J Am Coll Cardiol* 2000, **36:**2090–2095.
39. Dunselman PH for the Replacement of Angiotensin Converting Enzyme Inhibition (REPLACE) Investigators: **Effects of the replacement of the angiotensin converting enzyme inhibitor enalapril by the angiotensin II receptor blocker telmisartan in patients with congestive heart failure. The replacement of angiotensin converting enzyme inhibition (REPLACE) investigators.** *Int J Cardiol* 2001, **77:**131–138.
40. Tang WH, Vagelos RH, Yee YG, *et al.*: **Neurohormonal and clinical responses to high- versus low-dose enalapril therapy in chronic heart failure.** *J Am Coll Cardiol* 2002, **39:**70–78.
41. Campbell DJ, Aggarwal A, Esler M, Kaye D: **Beta-blockers, angiotensin II, and ACE inhibitors in patients with heart failure.** *Lancet* 2001, **358:**1609–1610.
42. Lonn EM, Yusuf S, Dzavilk V, *et al.*: **Effects of ramipril and vitamin E on atherosclerosis. The study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE).** *Circulation* 2001, **103:**919–925.
43. Reddy MS, Landa M, Stark PC, *et al.*, Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Disease (AIPRD) Study Group: **Antiproteinuric dose response of angiotensin-converting enzyme inhibitors in non-diabetic chronic kidney disease.** *J Am Soc Nephrol* 2002, **13:**264A.
44. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: **The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group.** *N Engl J Med* 1993, **329:**1456–1462.
45. Ravid M, Brosh D, Levi Z, *et al.*: **Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial.** *Ann Intern Med* 1998, **128:**982–988.
46. O'Hare P, Bilbous R, Mitchell T: **Low-dose ramipril reduces microalbuminuria in type 1 diabetic patients without hypertension: results of a randomized controlled trial.** *Diabetes Care* 2000, **23:**1823–1829.
47. Okada T, Toshiyuki N, Matsumoto H, *et al.*: **Renoprotective effect of combination with angiotensin converting enzyme inhibitor and angiotensin receptor blocker in diabetic nephropathy with renal failure.** *J Am Soc Nephrol* 2002, **13:**687A.
48.• 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:**601–606.

This study compared the dose-related effects of ARB versus ACE inhibitor therapy on the reduction in albuminuria in patients with diabetic nephropathy.

49.• Andersen S, Rossing P, Juhl TR, *et al.*: **Optimal dose of losartan for renoprotection in diabetic nephropathy.** *Nephrol Dial Transplant* 2002, **17:**1413–1418.

One of the few studies addressed the optimal dose of ARBs. In type 1 diabetes, 100 mg losartan was associated with the greatest renoprotection, the latter based on BP and proteinuria reduction.

50. Laverman GD, Steen Andersen, Peter Rossing, *et al.*: **Dose-dependent reduction of proteinuria by losartan does not require reduction of blood pressure.** *J Am Soc Nephrol* 2002, **13:**265A.
51. Jacobsen P, Andersen S, Jensen BR, Parving HH: **Additive effect of ACE inhibition and angiotensin II receptor blockade in type I diabetic patients with diabetic nephropathy.** *J Am Soc Nephrol* 2003, **14:**992–999.
52. Andersen NH, Mogensen CE: **Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers: evidence for and against the combination in the treatment of hypertension and proteinuria.** *Curr Hypertens Rep* 2002, **4:**394–402.
53. Bos H, Andersen S, Rossing P, *et al.*: **Role of patient factors in therapy resistance to antiproteinuric intervention in nondiabetic and diabetic nephropathy.** *Kidney Int* 2000, **75:**S32–S37.
54. Mogensen CE, Neldam S, Tikkanen I, *et al.*: **Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study.** *Br Med J* 2000, **321:**1440–1444.
55. de Pablos-Velasco PL, Pazos Toral F, Esmatjes JE, *et al.*: **Losartan titration versus diuretic combination in type 2 diabetic patients.** *J Hypertens* 2002, **20:**715–719.
56. Muirhead N, Feagan BF, Mahon J, *et al.*: **The effects of valsartan and captopril on reducing microalbuminuria in patients with type 2 diabetes mellitus: a placebo-controlled trial.** *Curr Ther Res* 1999, **60:**650–660.
57. Rossing K, Christensen PK, Jensen BR, Parving HH: **Dual blockade of the renin-angiotensin system in diabetic nephropathy: a randomized double-blind crossover study.** *Diabetes Care* 2002, **25:**95–100.
58.• Rossing K, Christensen PK, Hansen BV, *et al.*: **Optimal dose of candesartan for renoprotection in type 2 diabetic patients with nephropathy: a double-blind randomized cross-over study.** *Diabetes Care* 2003, **26:**150–155.

A comparative dose-response trial of the ARB candesartan was studied in patients with type II diabetes with macroalbuminuria.

59. Segura J, Campo C, Nieto J, *et al.*: **Positive simultaneous effect of candesartan dose up-titration on proteinuria and blood pressure.** *Am J Hypertens* 2003, In press.
60. Laverman GD, Henning RH, de Jong PE, *et al.*: **Optimal antiproteinuric dose of losartan in nondiabetic patients with nephrotic range proteinuria.** *Am J Kidney Dis* 2001, **38:**1381–1384.
61. *DROP (Diovan Reduction of Proteinuria) Study.* Basel, Switzerland: Novartis Pharmaceuticals; 2003.
62. *SMART (Supramaximal Doses of Atacand and Renal Therapy) Study.* Wilmington, DE: AstraZeneca Pharmaceuticals; 2003.
63. Weinberg MS, Haneiwich R, Weinberg AJ: **The safety and efficacy of supramaximal doses of candesartan cilexetil (160 mg) in subjects with a history of hypertension and chronic renal disease that are naive to angiotensin receptor blockade therapy.** *Am J Hypertens* 2003, **16:**4A.