Lowering of Proteinuria in Response to Antihypertensive Therapy Predicts Improved Renal Function in Late but Not in Early Diabetic Nephropathy: A Pooled Analysis

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Key Words

Hypertension • Microalbuminuria • Albuminuria •
Glomerular filtration rate • Diabetic nephropathy

Abstract

In late diabetic nephropathy (DN) the initial lowering of albumin excretion rate (AER) with antihypertensive therapy is proportional to the degree of subsequent preservation of glomerular filtration rate (GFR). Whether a similar relationship exists between AER and GFR in early diabetes is not known. The present analysis has compared AER and GFR responses to antihypertensive therapy in 33 published studies (77 treatment groups) of early and late DN in type 1 (T1) and type 2 (T2) diabetes, analyzed on an intention-to-treat basis. Prospective trials were included if the initial change in AER during the first year of therapy and the change in GFR during at least 2 years of follow-up could be estimated from group mean data. The initial % decreases in AER were 5.9 ± 4.3 (T1), 10.5 ± 5.4 (T2, normotensive) and 18.4 ± 6.2 (T2, hypertensive) in early DN and 7.6 ± 11.1 (T1) and 20.8 ± 5.5 (T2) in late DN. The corresponding annual % rates of decline of GFR were 2.0 ± 0.5 (T1), 1.6 ± 0.5 (T2, normotensive) and 2.1 ± 0.3 (T2, hypertensive) in early DN and 9.8 ± 1.5 (T1) and 9.2 ± 1.1 (T2) in late DN. AER and GFR responses in each treat-

ment group were closely correlated in late nephropathy (T1, $r = -0.67$, $p = 0.03$; T2, $r = 0.57$, $p = 0.02$) but not in early nephropathy. In contrast to late DN, the initial decrease in AER with antihypertensive therapy was not shown to predict the subsequent rate of decline of GFR in early DN. It follows that assessment of renoprotection during antihypertensive therapy in early nephropathy should be based not only on albuminuria but also on the GFR response.

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Introduction

Hypertension is both a cause and effect of renal impairment and its treatment influences renal outcomes. A meta-analysis of several large intervention studies has shown that a lower mean blood pressure during therapy is associated with slower rates of decline of glomerular filtration rate (GFR) [1]. However, attained blood pressure is not the only determinant of the rate of progression of renal impairment. For instance, the level of proteinuria and the reduction of proteinuria during antihypertensive therapy may also influence the rate of decline of renal function. An early reduction in proteinuria associated with hypertensive therapy was first shown to predict the

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long-term decline in GFR, using within patient comparisons, in two small studies of overt nephropathy in diabetic [2] and non-diabetic kidney disease [3, 4].

Subsequent studies of overt diabetic nephropathy using group mean data also support the concept that the early antiproteinuric response to antihypertensive therapy predicts the subsequent decline in renal function. In patients with type 1 diabetes and overt nephropathy, the Collaborative Study Group showed that captopril therapy, supplemented as necessary with other antihypertensive agents, resulted in a decrease in proteinuria of around 40% and an approximate halving of the rate of doubling of serum creatinine [5]. In patients with type 2 diabetes and late nephropathy, two large studies of angiotensin receptor blockade examined the independent role of proteinuria and changes in proteinuria as predictors of the subsequent rate of decline of renal function.

In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study [6], changes in albuminuria in the first 6 months of therapy with losartan were related to the degree of long-term renoprotection. A reduction in albuminuria of around 50% was associated with a 36% reduction in the risk of doubling of serum creatinine, ESRD or death [7]. This renoprotective effect was still demonstrable after controlling for the level of attained blood pressure. In the Irbesartan Diabetic Nephropathy Trial (IDNT) [8], for each halving of proteinuria during the first 12 months of therapy with irbesartan, amlodipine or placebo, the risk for renal failure was reduced by 56% [9]. Furthermore, multivariate analysis showed that proteinuria reduction in the first 12 months of irbesartan therapy accounted for 36% of the total renoprotective effect observed.

In early diabetic nephropathy (microalbuminuria), studies of antihypertensive therapy with ACE inhibitors have shown reductions in albumin excretion rate (AER) of >50% which are comparable in percentage terms to those reported in overt nephropathy. In hypertensive patients with type 1 diabetes and early nephropathy there was a 70% reduction of albuminuria during captopril therapy but no significant change in GFR was noted during 2 years of follow-up [10]. Similarly, a study of hypertensive patients with type 2 diabetes and early nephropathy showed a 70% reduction in albuminuria during treatment with irbesartan at a dose of 300 mg daily but no significant change in renal function over 2 years [11].

The above studies raise the question of whether the initial antialbuminuric response to antihypertensive therapy in early diabetic kidney disease can predict the rate of decline in GFR previously shown in studies of

overt nephropathy. The present analysis has therefore examined the degree of coupling of the albuminuric and GFR responses to antihypertensive therapy, using group mean data, on an intention-to-treat basis, in studies of at least 2 years duration in patients with early and late diabetic nephropathy.

Methods

Studies of antihypertensive therapy in early and late diabetic nephropathy were considered for inclusion in the analysis based on a Medline literature search (1966–September 2006) using the search strategy described by Strippoli et al. [12]. The present analysis was based on all references quoted in a meta-analysis of antihypertensive therapy in diabetes by Strippoli et al. A search for additional studies using references in papers quoted by Strippoli et al. was also performed. The criteria for inclusion of a study in the analysis were: (1) Prospective study of antihypertensive therapy in diabetic patients with at least 2 years of follow-up. (2) Inclusion of a parallel or sequential comparator group. (3) Sufficient data to allow estimation of the AER response as a percentage of baseline in the first year of follow-up. (4) Sufficient data to allow estimation of the annual rate of decline of GFR during the entire study.

All studies meeting these criteria were included in the analysis.

In the systematic review of antihypertensive therapy and diabetic nephropathy by Strippoli et al. [12], 24 of 59 studies met the above criteria. In addition, nine other studies were included. Inclusion was based on two main criteria. Firstly, if the change in albuminuria (AER or albumin creatinine ratio) or proteinuria during the first 12 months of therapy could be estimated from mean data for each treatment group on an intention-to-treat basis. Secondly, if the change in GFR during at least 2 years of follow-up could be estimated from group mean data.

All albuminuria data were expressed as $\mu\text{g}/\text{min}$, using the following equivalents: $200 \mu\text{g}/\text{min} = 300 \text{ mg}/24 \text{ h} = \text{total proteinuria}$ $500 \text{ mg}/24 \text{ h} = 300 \text{ mg}$ albumin per gram of creatinine [13]. The initial AER response was defined as percentage change in AER during the first 12 months of therapy. Hypertension was defined as resting blood pressure $>140/90 \text{ mm Hg}$.

For the purposes of this analysis, each study was categorized according to group mean data for baseline albuminuria and final GFR. In studies of type 1 diabetes, early diabetic nephropathy was defined as baseline AER between 30 and $300 \text{ mg}/24 \text{ h}$ and final $\text{GFR} >90 \text{ ml}/\text{min}$ or $>90 \text{ ml}/\text{min}/1.73 \text{ m}^2$. All 'microalbuminuria' studies were classified as early diabetic nephropathy, equivalent to CKD stage 1. The onset of the clinical phase of diabetic nephropathy is signalled, by convention, by the appearance of persistent proteinuria (total daily protein excretion of 0.5 g or more), which corresponds to an AER greater than about $200 \mu\text{g}/\text{min}$ (i.e. about $300 \text{ mg}/\text{day}$) [13]. Late diabetic nephropathy was therefore defined as baseline albuminuria $>300 \text{ mg}/24 \text{ h}$ or total proteinuria $>500 \text{ mg}/24 \text{ h}$ and final $\text{GFR} \leq 90 \text{ ml}/\text{min}$ or $\leq 90 \text{ ml}/\text{min}/1.73 \text{ m}^2$. All 'macroalbuminuria' studies were classified as late nephropathy, equivalent to CKD stage 2 or 3. One study in normotensive patients with type 1 diabetes, macroalbuminuria

and final GFR >90 ml/min [14] could not be classified and was therefore excluded from analysis.

In studies of type 2 diabetes, early and late nephropathy were defined according to baseline albuminuria as for type 1 diabetes and final GFR greater or less than 75 ml/min or 75 ml/min/1.73 m², respectively. The use of a lower GFR cut-off was based on the age-related decline in GFR in subjects with type 2 diabetes [15].

All microalbuminuria studies in type 2 diabetes were classified as early nephropathy, equivalent to CKD stage 1 or early stage 2. All macroalbuminuria studies in type 2 diabetes were classified as late nephropathy, equivalent to CKD late stage 2 or stage 3. One study in patients with type 2 diabetes, microalbuminuria and final GFR <75 ml/min/1.73 m² [16] and one study in patients with type 2 diabetes, macroalbuminuria and final GFR >75 ml/min [17] could not be classified and both were therefore excluded from analysis.

In all early nephropathy studies involving patients with type 1 diabetes (n = 9), proteinuria was assessed by AER. In studies of late nephropathy involving patients with type 1 diabetes (n = 5), proteinuria was assessed by AER in four studies and total proteinuria >0.5 g/24 h in one study. All studies of early nephropathy in normotensive (n = 5) or hypertensive (n = 8) patients with type 2 diabetes used AER to assess albuminuria. In studies of late nephropathy (n = 7) involving patients with type 2 diabetes, proteinuria was assessed by AER in three studies, albumin to creatinine ratio >30 (mg/g) in one study and total proteinuria >500 mg/24 h in three studies. The initial response of proteinuria to antihypertensive therapy was calculated as the percentage change in proteinuria in the first 3–12 months using group mean data.

GFR was measured by isotopic methods in 14 studies, by io-hexol in three studies, by inulin in one study and by creatinine clearance in 12 studies. GFR was estimated by the Cockcroft-Gault formula in two studies, and by the simplified four variable modification of diet in renal disease (MDRD) formula in one study. The annual percentage change in measured or estimated GFR was calculated from group mean data over 2–8 years using baseline GFR and the last value on therapy. To allow for variations in methods of reporting proteinuria and renal function in different studies, group mean changes in these parameters were calculated as a percentage of baseline values. Three large studies of late nephropathy [5, 6, 8] reported changes in total proteinuria and creatinine clearance or creatinine-based estimate of GFR. Percentage changes in these parameters were in agreement with other studies of late nephropathy, which used albuminuria and direct GFR measurements. In this analysis, the terms AER and GFR are therefore used in a generic sense to refer to renal endpoints in both early and late nephropathy. Initial % changes in AER and annual % changes in GFR were calculated in three categories of early nephropathy studies (type 1, type 2 normotensive, type 2 hypertensive) and two categories of late nephropathy studies (type 1 and type 2). Because the presence of hypertension influences both the design of intervention studies as well as the progression of nephropathy, studies in hypertensive patients with type 2 diabetes and early nephropathy were analyzed separately from those in normotensive patients.

The relationship between percentage changes in AER and GFR to mean arterial blood pressure (diastolic blood pressure and one third of pulse pressure) was also assessed. Changes in AER and GFR in each treatment group were related to final mean arterial pressure and to change in mean arterial pressure during the study.

Results

The effects of antihypertensive therapy were analyzed in 33 studies. Thirty-one studies were prospective, randomized studies of ACE inhibition or angiotensin receptor blockade with concurrent control groups allocated to other antihypertensive agents to minimize differences in attained blood pressure. Two early studies were within group studies before and during 'conventional' antihypertensive therapy [18, 19].

Table 1 summarizes the distribution of treatment groups according to diabetes type, stage of nephropathy and nature of intervention. An inhibitor of the renin-angiotensin system (RAS) was used in 31 of 77 treatment groups, with the majority being ACE inhibitors. The details of the 33 studies in the analysis are summarized according to study category in table 2a–e.

There were more early than late nephropathy studies in this analysis, but the three largest studies [5, 6, 8] were performed in late nephropathy (table 2). Mean study duration was comparable in early (4.0 ± 0.4 years) and late nephropathy studies (3.2 ± 0.4 years, $p = 0.15$).

Baseline albuminuria and GFR in the five study categories are shown in figure 1. There is clear separation of early and late studies according to baseline AER (fig. 1a) but there is overlap in baseline GFR (fig. 1b). This is the basis for the classification of stage of nephropathy according to final rather than baseline GFR.

The initial percentage changes in AER and the overall percentage changes in GFR are presented in five categories according to diabetes type and stage of nephropathy, as shown in figure 2. In type 1 diabetes studies, the initial decrease in albuminuria was $5.9 \pm 4.3\%$ in early and $7.6 \pm 11.1\%$ in late nephropathy ($p = 0.38$). In type 2 diabetes studies, the initial decrease in albuminuria was similar in hypertensive and in normotensive early nephropathy ($18.4 \pm 6.2\%$ vs. $10.5 \pm 5.4\%$, $p = 0.38$). The initial decrease in albuminuria in late type 2 nephropathy was $20.8 \pm 5.5\%$ ($p = 0.21$ vs. early normotensive, $p = 0.78$ vs. early hypertensive).

The rates of annual decline in GFR expressed as ml/min or ml/min/1.73 m² for the five study groups according to diabetes type, presence or absence of hypertension and early or late stage nephropathy are shown in table 3. Because of differences in baseline renal function, rates of decline in GFR in early and late nephropathy were expressed in absolute terms before comparisons were made. In both type 1 and type 2 diabetes, the absolute rate of decline of GFR was greater in late than in early nephropathy studies.

Table 1. Classification of study groups according to type of antihypertensive therapy

Intervention	Type 1 early	Type 1 late	Type 2 early NT	Type 2 early HT	Type 2 late	Treatment groups	Subjects
ACE _i	11	3	4	5	4	27	1,109 ¹
ARB				2	2	4	1,719
CCB	3		1	2	3	9	935 ¹
Standard (incl. BB, diuretic)	0	3	0	1	3	7	98
Standard + placebo		1		3	2	6	1,767
Placebo only	8		4			12	397
Untreated	1	3				4	51
Moderate			1	2	1	4	416 ¹
Intensive			1	2	1	4	413 ¹
Treatment groups (total = 77)	23	10	11	17	16		
Studies (total = 33)	9	5	5	7	7		
Subjects	681	510	407	1,804	3,503		6,905 ¹

¹ ABCD study (n = 470 patients) shown twice.

ACE_i = ACE inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; Standard = non-ACE_i, non-ARB, non-CCB including β-blockers (BB) and diuretics; Moderate, intensive = levels of blood pressure control as defined for early nephropathy in the ABCD trial [40] and for late nephropathy by Joss et al. [43].

Table 2a. Normotensive type 1, early DN

Author	Study duration years	Intervention										GFR method	PP	Mean baseline GFR	
		Δ AER %	n	Δ GFR %	Δ AER %	n	Δ GFR %	Δ AER %	n	Δ GFR %	ml/min/1.73 m ²			ml/min	
Mathiesen 1991 [44] 1999 [45]	8	12	untreated 23	-0.5	-2.1	captopril 21	-1.1					⁵¹ Cr-EDTA	AER		128
Hansen 1994 [46]	2	13.1	placebo 12	-1.9	-1.9	captopril 10	-0.7					¹²⁵ I-iotha-lamate	AER	133	
Microalbumi- nuria Captopril Study Group 1996 [10]	2	2	placebo 114	-6.7	-30	captopril 111	-1.5					CC	AER	95	
Crepaldi 1998 [47]	3	11.7	placebo 34	-1.5	-15.4	lisinopril 32	-1.2			nifedipine 26		⁵¹ Cr-EDTA	AER	116	
Atlantis 2000 [48]	2	0	placebo 46	1.75	-20	ramipril (1.25 mg) 44 -0.7				ramipril (5 mg) 44 -3.4		iohexol	AER		104
Esprit 2001 [49]	3	-45	enalapril 18	-4.1	25	nifedipine 18 -4.1				0	placebo 18 -4.1	iohexol	AER	103	
Jerums 2001 [50]	3	-45	perindopril 13	1.0	17.5	nifedipine 10 7.4				27.6	placebo 10 -1.3	^{99m} Tc-DTPA	AER	103	
Bojestig 2001 [51]	2	0	placebo 18	-2.8	0.9	ramipril (1.25 mg) 19 -2.5				-13	ramipril (5 mg) 18 2.0	iohexol	AER	103	
Poulsen 2001 [52]	2	10	placebo 10	1.2	-23	lisinopril 12 2.2						¹²⁵ I-iotha-lamate	AER	133	

PP = Proteinuria parameter; CC = creatinine clearance; n = number of patients; Δ AER % = initial percentage change in AER or equivalent during first year of study; Δ GFR % = annual percentage change in GFR or equivalent assessed over entire study period.

Table 2b. Normotensive type 2, early DN

Author	Study duration years	Intervention						GFR method	PP	Mean baseline GFR	
		Δ AER %	n	Δ GFR %	Δ AER %	n	Δ GFR %			ml/min/1.73 m ²	ml/min
Sano 1994 [53]	4	6.1	placebo 12	-0.9	-29.4	enalapril 12	1.3	CC	AER		91
Ahmad 1997 [54]	5	0	placebo 51	-0.8	-12.7	enalapril 52	-0.8	insulin	AER	124	
Ravid 1998 [55]	6	8.9	placebo 79	-2.6	-14.7	enalapril 77	-0.2	CC	AER	108	
Schrier 2002 [42] ABCD	5	0	moderate 60	-3.3	-26	intensive 49	-2.3	CC	AER	85	
Jerums 2004 [32]	6	-4.75	perindopril 23	-2.6	-9	nifedipine 27	-1.5	^{99m} Tc-DTPA	AER	92	
						8	placebo 27			-4.3	

PP = Proteinuria parameter; CC = creatinine clearance; n = number of patients; Δ AER % = initial percentage change in AER or equivalent during first year of study; Δ GFR % = annual percentage change in GFR or equivalent assessed over entire study period.

Table 2c. Hypertensive type 2, early DN

Author	Study duration years	Intervention						GFR method	PP	Mean baseline GFR	
		Δ AER %	n	Δ GFR %	Δ AER %	n	Δ GFR %			ml/min/1.73 m ²	ml/min
Lacourciere 1993 [56]	3	-77	captopril ± HCT 9	-2.10	-46	metoprolol ± HCT 12	-0.4	⁵¹ Cr-EDTA	AER	93	
Sano 1994 [53]	4	14.6	placebo 13	-0.8	-16.7	enalapril 11	1.2	CC	AER	90	
Chan 2000 [57]	5.5	-54	enalapril 50	-3.5	11	nifedipine 52	-3.4	CC	AER	75	
Parving (RMA-2)	2	-2	placebo 201	-2.4	-2.4	irbesartan (150 mg) 195	-2.7	CC	AER	109	
						irbesartan (300 mg) 194	-3.2				
Estacio 2000 [58] ABCD	5	-26	moderate 233	-2.5	-18	intensive 237	-1.7	CC	AER	85 ¹	
Estacio 2000 [58] ABCD	5	-33	enalapril 234	-1.9	0	nisoldipine 231	-1.8	CC	AER	85 ¹	
Gaede 1999 [26] 2003 [25]	8	3.8	standard 80	-2.9	-7.4	intensive 80	-2.5	⁵¹ Cr-EDTA	AER	117	
Nankervis 1998 [59]	3	-16.8	perindopril 20	-2.9	16.4	placebo 20	-2.1	CG	AER	94	

PP = Proteinuria parameter; CC = creatinine clearance; n = number of patients; Δ AER % = initial percentage change in AER or equivalent during first year of study; Δ GFR % = annual percentage change in GFR or equivalent assessed over entire study period.

¹ At baseline, the relative proportion of participants in the ABCD study (hypertensive arm) was normo 49%, micro 32% and macro 19%, with an overall mean AER of 32 μg/min.

Table 2d. Type 1, late DN

Author	Study duration years	Intervention									GFR method	PP	Mean baseline GFR	
		Δ AER %	n	Δ GFR %	Δ AER %	n	Δ GFR %	Δ AER %	n	Δ GFR %			ml/min/1.73 m ²	ml/min
Mogensen 1982 [18]	6.1	25.8	5	pre-R _x -16.6	1.6	5	during R _x ¹ -6.2				¹²⁵ I-iothalamate	AER		86
Parving 1987 [19]	2 years (pre) 6 years (post)	50.0	10	pre-R _x -11.2	-38.0	10	metrop/frus/HCT -4.0				⁵¹ Cr-EDTA	AER	102 (pre-Tx) 80 (Tx gp)	
Parving 1988 [60]	2.3	5.0	13	untreated -10.4	-39.0	18	captopril -5.9				⁵¹ Cr-EDTA	AER	97	
Bjorck 1992 [61]	2.25	10.7	18	metoprolol $\pm$ frus -11.7	-68.8	22	enalapril $\pm$ frus -4.3				⁵¹ Cr-EDTA	AER	47	
Lewis 1993 [5]	2.7	2.0	202	placebo + conv'l -17.0	-25.0	207	captopril + conv'l -11.0				CC	total proteinuria		82

PP = Proteinuria parameter; CC = creatinine clearance; n = number of patients; Δ AER % = initial percentage change in AER or equivalent during first year of study; Δ GFR % = annual percentage change in GFR or equivalent assessed over entire study period; pre-R_x = pretreatment; during R_x = during treatment; conv'l = conventional.

¹ Propranolol or metoprolol, $\pm$ hydralazine, prazosin or frusemide.

Table 2e. Type 2, late DN

Author	Study duration years	Intervention									GFR method	PP	Mean baseline GFR	
		Δ AER %	n	Δ GFR %	Δ AER %	n	Δ GFR %	Δ AER %	n	Δ GFR %			ml/min/1.73 m ²	ml/min
Lebovitz 1994 [62]	3	-4.4	18	conventional -14.8	-44.7	28	enalapril -11.0				¹²⁵ I-iothalamate	total proteinuria	61	
Nielsen 1997 [22]	3.5	-4.5	17	lisinopril -10.7	-12	19	atenolol -9.7				⁵¹ Cr-EDTA	AER	74	
Bakris 1996 [35]	5.3	-11.9	16	atenolol -5.7	-43.3	18	NDH-CCB -2.4	-65	18	lisinopril -1.5	CC	total proteinuria	61	
Fogari 1999 [21]	2	-34.8	26	ramipril -4.3	-21.5	25	nitrendipine -2.8				CC	AER		44
Lewis 2001 [8] IDNT	2.6	-33	579	irbesartan -12	-6	567	amlodipine -15	10	569	placebo + conv'l -14	CC	total proteinuria		45
Brenner 2001 [6] RENAAL	3.4	-30	751	losartan -11	5	762	placebo + conv'l -13				eGFR	ACR		40
Joss 2004 [43]	2	6.6	43	moderate -11.1	-4	47	intensive -8				C-G	AER		55

PP = Proteinuria parameter; CC = creatinine clearance; n = number of patients; Δ AER % = initial percentage change in AER or equivalent during first year of study; Δ GFR % = annual percentage change in GFR or equivalent assessed over entire study period.

Fig. 1. Baseline renal parameters. **a** AER = Baseline albumin excretion rate or equivalent in individual study groups. 200 $\mu\text{g}/\text{min}$ = AER 300 $\text{mg}/24\text{ h}$ = total proteinuria 500 $\text{mg}/24\text{ h}$ = 300 mg albumin per gram of creatinine. **b** GFR = Baseline glomerular filtration rate in individual study groups. $\circ$ = GFR $\text{ml}/\text{min}/1.73\text{ m}^2$, $\bullet$ = GFR ml/min , NT = normotensive, HT = hypertensive.

In five studies with 10 treatment groups of type 1 diabetes and late nephropathy, there was a close relationship between initial change in albuminuria during the first year and the mean rate of decline in GFR during the whole study in each treatment group ($r = -0.67$, $p = 0.034$) (fig. 3). The percentage changes in AER and GFR were also compared by a weighted comparison of means to allow for differences in sample size [20]. This showed that the weighted mean initial change in AER was -12.7% , and the weighted mean overall change in GFR was -12.8% . In seven studies with 16 treatment groups of patients with type 2 diabetes and late nephropathy, there was a significant relationship between initial change in albuminuria and the overall mean rate of decline in GFR for each study group ($r = -0.57$, $p = 0.02$) (fig. 4). The weighted mean initial change in AER was -11.8% and the weighted mean overall change in GFR was -12.5% .

In contrast with results in late nephropathy, studies of antihypertensive therapy in early nephropathy did not show a significant relationship between initial changes in albuminuria and long-term changes renal function. As shown in figure 3, in nine studies with 23 treatment groups in normotensive patients with type 1 diabetes and early nephropathy, there was no significant relationship between initial changes in albuminuria and long-term change in GFR ($r = -0.10$, $p = 0.33$). In five studies with 11 treatment groups in normotensive patients with type

2 diabetes and early nephropathy (fig. 4), there was also no significant relationship between initial changes in albuminuria and long-term rate of decline in GFR ($r = -0.18$, $p = 0.30$). In seven studies with 17 treatment groups of hypertensive patients with type 2 diabetes and early nephropathy (fig. 4), initial changes in albuminuria were not significantly related to long-term change in GFR ($r = +0.02$, $p = 0.47$).

In order to further clarify the contribution of RAS inhibitor treatment groups and their corresponding control or comparator groups, studies of late nephropathy in type 1 diabetes and late nephropathy in type 2 diabetes have been replotted to show the relationship of each RAS inhibitor study with the corresponding control or comparator group (fig. 5).

Because of limitations due to small numbers of study groups, it is difficult to separate RAS inhibitor studies from the rest. However, the overall trend of the data suggests that the relationship between Δ AER and Δ GFR is not necessarily class-specific. For instance, two small studies performed in the 1980s by Mogensen [18] and Parving et al. [19] showed marked attenuation of GFR decline after commencement of non-RAS inhibitor therapy.

The relationship between mean arterial pressure, expressed as final attained pressure or % decline during the study, and rate of annual decline of GFR was also assessed. No significant relationship was observed between

Fig. 2. Initial changes in AER and annual changes in GFR according to diabetes type and stage of nephropathy. **a** % Δ AER = Percentage change in albuminuria or equivalent in individual study groups during first year of study (mean $\pm$ SEM). **b** % Δ GFR = Annual percentage change in GFR or equivalent in individual study groups, assessed over the entire study period (mean $\pm$ SEM).

Fig. 3. Relationship between initial change in AER and overall change in GFR per year in type 1 diabetes. **a** Mean data from 23 study groups in 9 studies of type 1 diabetes and early diabetic nephropathy are shown. **b** Mean data from 10 study groups in 5 studies of type 1 diabetes and late diabetic nephropathy are shown.

Fig. 4. Relationship between initial change in AER and overall change in GFR per year in type 2 diabetes. **a** Mean data from 11 study groups in 5 studies of type 2 diabetes and normotensive early diabetic nephropathy are shown. **b** Mean data from 17 study groups in 7 studies of type 2 diabetes and hypertensive early diabetic nephropathy are shown. **c** Mean data from 16 study groups in 7 studies of type 2 diabetes and late diabetic nephropathy are shown.

Table 3. Absolute rates of decline of GFR according to study category

	Type 1 early	Type 2 early NT	Type 2 early HT	Type 1 late	Type 2 late
Δ GFR, ml/min/year	0.94 ± 0.87 (n = 5)	$0.63 \pm 0.79^{**}$ (n = 4)	$1.58 \pm 0.61^{**}$ (n = 6)	10.35 ± 1.57 (n = 4)	4.68 ± 0.65 (n = 9)
Δ GFR, ml/min/1.73 m ² /year	$2.42 \pm 0.57^{**}$ (n = 18)	$2.09 \pm 0.44^*$ (n = 7)	$2.21 \pm 0.29^{**}$ (n = 11)	6.26 ± 1.47 (n = 6)	5.32 ± 1.27 (n = 7)

n = Number of study groups.

* $p < 0.05$ vs. corresponding late; ** $p < 0.01$ vs. corresponding late.

Fig. 5. Relationship between change in AER and overall change in GFR per year in studies of late nephropathy according to type of antihypertensive therapy in type 1 diabetes (a) and type 2 diabetes (b). Treatment groups for each study are linked by a solid line.

any of these parameters and rate of decline of GFR in early nephropathy. In a small number of study groups of late nephropathy in type 1 diabetes, there was a correlation between final mean arterial pressure and annual change in GFR expressed as ml/min/1.73 m² ($r = -0.92$, $p < 0.01$, $n = 6$). The corresponding correlation was not significant in studies of late nephropathy in type 2 diabetes. In 14 study groups of late nephropathy in type 2 diabetes, the change in mean arterial pressure during the study was correlated with the percentage change in GFR ($r = -0.56$, $p < 0.05$), but this correlation was not significant in studies of late nephropathy in type 1 diabetes.

Discussion

In studies of late nephropathy in both type 1 and type 2 diabetes, this analysis demonstrates a strong association between initial changes in albuminuria and overall changes in GFR during antihypertensive therapy. This is consistent with the concept that proteinuria itself is a major progression promoter in established diabetic nephropathy [23].

In contrast with the results in late nephropathy, there was no significant relationship between the initial AER and overall GFR responses in studies of early diabetic nephropathy. This raises the possibility that treatment-related decreases in albuminuria in early nephropathy, with normal or near-normal GFR, represent functional and presumably reversible changes in renal albumin handling and/or GFR, which may be independently modulated.

Because of disparities in study size, it was important to determine if data obtained in larger studies were representative of the overall results obtained. The captopril study by the Collaborative Study Group [5] assessed the effects of captopril in over 400 patients with type 1 diabetes and late nephropathy and was consistent with the general trend of results in other studies in this category (fig. 3). Results from over 1,500 patients with type 2 diabetes in the IDNT study [8] and over 1,400 patients with type 2 diabetes in the RENAAL study [6] were also consistent with the overall results shown in studies of type 2 diabetes and late nephropathy (fig. 4). AER and GFR responses, expressed as weighted means, were almost identical in studies of late nephropathy in type 1 and type 2

diabetes. This implies similar pathogenetic relationships between AER and GFR during overt nephropathy in both types of diabetes.

In early diabetic nephropathy, results from two large studies reflected the overall results. The microalbuminuria captopril study in normotensive patients with type 1 diabetes and microalbuminuria with over 100 participants, showed that an initial decrease in albuminuria of 30%, similar to that documented in percentage terms in patients with overt nephropathy, was not associated with a significant decrease in GFR over 2 years when assessed by creatinine clearance [10]. A sub-study using isotopic determination of GFR showed similar results [24]. In the IRMA 2 study of hypertensive patients with type 2 diabetes and microalbuminuria, an initial decrease of 38% in AER in patients treated with irbesartan 300 mg per day was not associated with a significant change in creatinine clearance over two years [11].

The longest study of intensive therapy in hypertensive patients with type 2 diabetes and microalbuminuria was performed over 8 years in 160 patients in the STENO-2 study [25]. Intensive multifactorial intervention focusing on antihypertensive therapy, glycemic control and control of dyslipidemia, was shown to nearly halve the rate of progression to macroalbuminuria when compared with results of standard therapy [26]. However, despite a follow-up of 8 years, the rate of decline of GFR of around 3 ml/min/year was similar in the intensively treated group and the group receiving standard therapy [25]. Analysis of the antialbuminuric response and the long-term GFR response within each study group by intention-to-treat analysis was representative of the general trend of data for hypertensive patients with microalbuminuria and type 2 diabetes. By contrast, a post-hoc analysis of pooled data for the intensive and standard groups showed that patients progressing from micro- to macroalbuminuria had a greater rate of decline of GFR over 8 years compared with patients who remained microalbuminuric or who regressed to normoalbuminuria [27]. The results of the STENO-2 study indicate that early decreases in AER during multifactorial intervention in hypertensive patients with microalbuminuria and normal or near-normal baseline GFR are not necessarily reflected in a slower rate of decline in GFR when examined prospectively on an intention-to-treat basis over 8 years [25]. This is consistent with the results of other studies in early nephropathy.

The failure to demonstrate a link between changes in albuminuria and renal function during antihypertensive therapy in early nephropathy studies may be due to limi-

tations in study design or to biological factors. In support of study design as an explanation is the slow rate of decline of GFR in early nephropathy, which may lead to errors in estimation or measurement of changes in GFR. However, the failure to show prospectively that changes in AER in the STENO-2 study [25] predict long-term decline in GFR in hypertensive microalbuminuric patients over 8 years argues against this. In this study, there were equal numbers of cardiovascular deaths over 8 years (7/80) in the groups receiving conventional or intensive therapy. Nevertheless, studies longer than this may be confounded by survival bias due to cardiovascular deaths.

A biological explanation for the lack of correlation between albuminuria response and rate of decline in GFR could be provided by differences in renal protein handling mechanisms in early compared with late nephropathy, even though percentage changes in AER were similar in hypertensive patients with type 2 diabetes with early and late nephropathy. In early nephropathy, initial changes in AER induced by antihypertensive agents are likely to reflect predominantly functional changes in glomerular and renal tubular handling of albumin by nephrons that are near-normal structurally [28]. The increase in AER shortly after cessation of renin angiotensin inhibition in studies of microalbuminuric patients supports this explanation [29–33]. Further evidence in support of independent regulation of AER and GFR in early nephropathy in patients with type 2 diabetes has been provided by the United Kingdom Prospective Diabetes Study [34]. In that study, early increases in AER and decreases in GFR occurred simultaneously in 14% and independently in around 40% of patients when evaluated over 15 years from diagnosis.

The present analysis suggests that uncoupling of AER and GFR also occurs in an interventional context in patients with type 2 diabetes and early nephropathy. Previous studies with verapamil in hypertensive patients with type 2 diabetes lend support to the concept that the nature of the AER response to antihypertensive therapy differs before and after the onset of overt nephropathy. For instance, in patients with overt nephropathy, verapamil decreased proteinuria and ameliorated the rate of decline of renal function [35]. By contrast, in normoalbuminuric patients, verapamil had no effect in preventing the onset of microalbuminuria in a placebo-controlled study over 4 years [36].

In later stages of nephropathy, changes in AER and GFR are less reversible and are associated with renal ultrastructural damage. Antihypertensive therapy in late nephropathy induces early hemodynamic and later ul-

trastructural effects. Early changes include lowering of intraglomerular pressure [37] and modulation of the glomerular filtration barrier by nephrin and other components of the slit pore diaphragm [38]. Renal ultrastructural changes could reflect a direct pathogenetic link between AER and GFR, but it is also possible that changes in AER and GFR are concurrent and not causally related. A direct pathogenetic role for renal tubular uptake of albumin has been proposed as a mediator of renal damage and eventual loss of renal function [23]. Reduction in AER by antihypertensive therapy would therefore be expected to reduce the rate of decline of GFR. A further consideration is that changes in AER reflect not only glomerular filtration of albumin but also renal tubular processing of albumin [39] whereas changes in GFR reflect alterations in renal hemodynamic and/or glomerular ultrastructure [28]. These diverse effects may not be directly linked to each other in a causal sense. However, there is experimental and clinical evidence to show that AER and GFR are both modulated by angiotensin [40].

It is important to note that changes in blood pressure occurred concurrently with changes in AER and GFR in all studies. It follows that initial changes in AER reflect a combination of systemic and intrarenal effects of antihypertensive therapy. Both effects are likely to contribute to the long-term rate of decline of GFR in studies of late diabetic nephropathy.

This study has several potential methodological limitations. Firstly, it is based on a post-hoc analysis of group mean data in studies ranging over 30 years from the earlier studies in the late 1970s. Ideally, individual subject data from all eligible studies should have been included in a formal meta-analysis. This was not possible because of methodological differences in assessing proteinuria and in measuring or estimating GFR.

A further problem is the slow rate of GFR decline in early diabetic nephropathy. Most studies of early nephropathy were performed with follow-up of 2–4 years. In some of these, the rate of decline of GFR was close to

the age expected decline in GFR in older patients. The design of future studies should recognize not only duration of follow-up but also evidence of progressive decline in renal function.

In order to achieve greater understanding of the relationship between albuminuria and GFR during antihypertensive therapy, further long-term studies are required in patients with GFR in the range of 90–45 ml/min (CKD stage 2 and early 3). This indicates CKD that is more advanced than in most previous studies of microalbuminuria but less advanced than in previous studies of established nephropathy. Accurate measurement of rates of decline of GFR in such patients would help to define the full spectrum of renal responses to RAS inhibitors and other antihypertensive agents. This is less easily achieved in endpoint studies, which focus on fast trackers by assessing rates of conversion from micro- to macroalbuminuria or rates of doubling of serum creatinine [41].

In summary, this analysis of 12 studies (26 treatment groups) of antihypertensive therapy in late diabetic nephropathy confirms that the initial decrease in AER can be used as a predictor or surrogate for the subsequent rate of decline of GFR. By contrast, this relationship could not be demonstrated on an intention-to-treat basis in 21 studies (51 treatment groups) of early nephropathy with a follow-up of 2–8 years. This implies a change in the relationship between AER and GFR as nephropathy progresses from early to late stages. It follows that assessment of renoprotection during antihypertensive therapy of early diabetic nephropathy should be based not only on albuminuria but should also include evaluation of the GFR response.

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