

Initial Angiotensin Receptor Blockade-Induced Decrease in Albuminuria Is Associated With Long-Term Renal Outcome in Type 2 Diabetic Patients With Microalbuminuria

A post hoc analysis of the IRMA-2 trial

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OBJECTIVE—We aimed to investigate the individual impact of initial responses in urinary albumin excretion (UAE) and systolic blood pressure (SBP) to angiotensin II receptor blocker (ARB) treatment on long-term renal outcome in patients with type 2 diabetes and microalbuminuria.

RESEARCH DESIGN AND METHODS—In a post hoc analysis of the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA)-2 trial we first assessed the individual variability in UAE and SBP response (0–6 months) in 531 subjects. Subsequently, we analyzed the individual effect of both response parameters on renal outcome defined as change in estimated glomerular filtration rate (eGFR) during 2 years of follow-up.

RESULTS—The median reductions in UAE and SBP in the population were –18% and –11 mmHg, respectively. In irbesartan-treated patients, 85 (24.4%) had a robust (>median) reduction in UAE but not in SBP (discordant SBP response) and 67 (19.3%) had a robust (>median) reduction in SBP but not in UAE (discordant UAE response). The degree of reduction in UAE was independently associated with the rate of eGFR decline ($P = 0.0037$). SBP showed a similar trend ($P = 0.087$). The relation between a larger UAE reduction and a slower rate of renal function decline was present in both cohorts with a SBP change above and below the median.

CONCLUSIONS—Within an individual, UAE response to ARB therapy may be discordant from SBP response. The initial change in UAE was independently associated with eGFR slope; the more UAE reduction the less eGFR decline, irrespective of the SBP change. These results suggest that in microalbuminuric patients with type 2 diabetes, UAE should be monitored after initiation of therapy and a separate target for renoprotective therapy.

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Current treatment strategies in diabetes separately target risk factors for micro- and macrovascular complications. HbA_{1c} is targeted with antidiabetic

agents, cholesterol levels with statins, and blood pressure (BP) with antihypertensive agents. Agents blocking the renin-angiotensin-aldosterone system (RAAS) are

first choice antihypertensives in patients with diabetes since these agents not only lower BP but also lower urinary albumin excretion (UAE), another important renal risk factor (1,2). Current guidelines recommend dose-titration of RAAS blockade on BP response to achieve a systolic BP (SBP) below 130 mmHg, without taking the response in UAE into account (3).

It is known that the initial response in proteinuria during RAAS blockade independently determines renal outcome in patients with diabetes and proteinuria (4). Moreover, recent studies have illustrated that within an individual, the response in BP is not always paralleled by a response in proteinuria or vice versa (5). These so-called discordant responses allow a, albeit retrospective, look at whether the response of BP, proteinuria, or their combination is the driving parameter for renoprotection. Data in patients with proteinuria have demonstrated that long-term renoprotection is mainly achieved in those patients with an initial fall in proteinuria irrespective of the BP response. Accordingly, this suggests that a treatment approach solely focusing on BP reduction may not be the most efficacious way to achieve renoprotection (6–8). Whether responses in albuminuria irrespective of BP relate to long-term renoprotection in patients with microalbuminuria has not been published.

We therefore performed a post hoc analysis in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) trial (9), investigating the variability in initial treatment responses in UAE and SBP in patients with type 2 diabetes and microalbuminuria. Second, we aimed to determine the impact of different UAE and SBP responses on renal outcome. This should provide insight as to

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whether albuminuria should be considered a target for renoprotective therapies in addition to BP in microalbuminuric patients.

RESEARCH DESIGN AND METHODS

The IRMA-2 study was a 2-year multicenter, randomized, double-blind trial in patients with type 2 diabetes and microalbuminuria comparing irbesartan (150 or 300 mg once daily) versus placebo on top of conventional antihypertensive treatment. The design of the study has been reported elsewhere (9). In brief, eligible patients had their antihypertensive agents discontinued during the run-in period and replaced by placebo. After 3 weeks, patients were randomly assigned to receive irbesartan 150, 300 mg, or matching placebo once daily. A total of 590 patients were followed for 2 years for the development of overt nephropathy. Patients were seen at month 3, 6, and every 6 months thereafter. Additional BP lowering medication, apart from ACE inhibitors and angiotensin II receptor blockers (ARBs), was allowed to reach the target BP of 135/85 mmHg. The study protocol was in accordance with the declaration of Helsinki and was approved by all local institutional review boards. All patients gave written informed consent.

Patients

IRMA-2 enrolled hypertensive patients with type 2 diabetes, ranging in age from 30 to 70 years. All patients had persistent microalbuminuria, which was defined as a UAE rate of 20 to 200 $\mu\text{g}/\text{min}$ in at least two out of three consecutive, sterile, overnight urine samples. The main exclusion criteria were a serum creatinine concentration >1.5 mg/dL (133 μmol per liter) for men and >1.1 mg/dL (97 μmol per liter) for women, nondiabetic kidney disease, cancer, life-threatening disease with death expected to occur within 2 years, and an indication for ACE inhibitors or ARBs.

Measurements

The urinary albumin concentration was determined by nephelometry at a central laboratory (10). The serum creatinine concentration was determined by Jaffe reaction with the use of a Hoffmann–LaRoche kit (11). Estimated glomerular filtration rate (eGFR) was estimated with the Modification of Diet in Renal Disease study equation (12). The lowest arterial BP during a 24-h period (Korotkoff phase I/IV) was measured twice in the sitting position after at least 10 min of rest.

BP and UAE response

This post hoc analysis focuses on the UAE and SBP change from baseline to month 6. A robust decline in UAE or SBP was defined as a decline in UAE or SBP more than the population median and was calculated as $100 \cdot \log(\text{UAE at 6 months}/\text{UAE at baseline})$. SBP change was calculated as the difference between the month 6 and baseline value. UAE change at month 6 for each patient. The month 6 values were chosen for two reasons: 1) the treatment effects were considered to be fully present at month 6, and 2) this was the earliest time point at which most variables of interest were available.

Patients were divided into groups according to the median of UAE and SBP change from baseline to month 6. Patients with both UAE change and SBP change above or below the median were considered to have a concordant response, whereas patients with either a UAE change or SBP change above the median were considered to have a discordant response.

Renal end points

Transition from micro- to macroalbuminuria (development of overt nephropathy) was the primary efficacy measure in the IRMA-2 trial, which was defined as UAE >200 $\mu\text{g}/\text{min}$ and at least 30% higher than baseline level of UAE on at least two out of three consecutive samples. Because the initial reduction in albuminuria induced by ARB treatment is directly related to the primary efficacy measure (which includes the long-term change in albuminuria), we decided to use the course of decline in eGFR from month 6 to end of follow-up as our primary renal end point. We looked at development of overt nephropathy in a secondary analysis.

Statistical analysis

Categorical variables are reported as frequencies and percentages. Variables with normal distribution are presented as mean with SD, and variables with a skewed distribution are presented as median with interquartile range. Non-normally distributed variables were log-transformed before analyses. Graphical methods and normality tests were used to ascertain normalization of the distribution after transformation. Differences between groups were tested with Fisher exact test for categorical variables and ANOVA for continuous variables, followed, where applicable, by post hoc Bonferroni correction for multiple testing.

A multivariate mixed model with random intercepts and random slopes was used to assess the relationship between the magnitude of SBP and UAE change and the rate of eGFR decline. Such a model calculates renal function decline over time within and between individuals also taking into account the correlation within individuals and time. For exploration of the relationship between the month 6 change in UAE and eGFR decline, the change in UAE was categorized according to quartiles and related to eGFR decline from month 6. The multivariate mixed model included the following baseline covariates: age, sex, log-transformed UAE, SBP and diastolic BP, eGFR, HbA_{1c}, duration of diabetes, total cholesterol, smoking, BMI, and treatment allocation. A multivariate Cox proportional hazards model was used to assess the relationship between the magnitude of UAE and SBP change from baseline to 6 months and time to development of overt nephropathy from 6 months to the end of follow-up. The multivariate Cox proportional hazards model included the same covariates as the above-mentioned multivariate mixed model. The initial fall in eGFR after start of treatment may reflect a hemodynamic response and may be associated with long-term renoprotection (13,14). Because the month 6 change in eGFR was not associated with the initial change in UAE and SBP, we considered the initial eGFR change not a potential confounder in our analyses. Relative risk reductions are described in the text as percent reductions ($[1 - \text{hazard ratio}] \times 100$). A *P* value ≤ 0.05 indicated statistical significance. Data were analyzed with SPSS version 18.0 (SPSS Inc., Chicago, IL) and SAS (SAS Institute, Cary, NC).

RESULTS

UAE and SBP change

A total of 531 out of 590 randomized patients had UAE and SBP measurements available at baseline and at 6 months postrandomization and were included in this post hoc analysis. The median responses in UAE and SBP in the population were 18% and 11 mmHg, respectively. We subsequently divided the population according to the median response in these parameters, defining a robust response as a response more than the population median. The median decline in UAE and SBP in each subgroup is reported in Table 1. In irbesartan-treated patients, 24.4% had a robust reduction in UAE

Table 1—Baseline characteristics of the patients stratified by groups of change in albuminuria and SBP from baseline to month 6

Characteristics	Concordant (negative) UAE <median* SBP <median**	Discordant UAE <median* SBP >median**	Discordant UAE >median* SBP <median**	Concordant (positive) UAE >median* SBP >median**
<i>n</i>	153	112	120	146
Changes 0–6 months				
Median interquartile change UAE (%)	35 (7–92)	35 (0–85)	–48 (–63 to –33)	–51 (–68 to –37)
Median interquartile change SBP (mmHg)	0 (–7 to 5)	–21 (–28 to –15)	–5 (–9 to 5)	–21 (–28 to –16)
Demographic characteristics				
Age (years)	58.3 ± 8.1	58.7 ± 8.6	57.9 ± 7.5	57.1 ± 8.2
Male sex, <i>n</i> (%)	104 (68.0)	82 (73.2)	77 (64.2)	100 (68.5)
Race, <i>n</i> (%)				
White	148 (96.7)	110 (99.1)	117 (98.3)	141 (96.6)
Nonwhite	5 (3.3)	1 (0.9)	2 (1.7)	2 (1.4)
Clinical characteristics				
BMI (kg/m ²)	29.9 ± 4.2	29.9 ± 4.1	30.4 ± 4.2	30.0 ± 4.2
Known duration of diabetes >5 years, <i>n</i> (%)	112 (73.2)	80 (71.4)	82 (68.3)	100 (68.5)
Smoking, <i>n</i> (%)	24 (15.7)	22 (19.6)	20 (16.7)	31 (21.2)
Laboratory variables				
Glycated hemoglobin (%)	7.4 ± 1.7	7.1 ± 1.6	7.1 ± 1.7	7.2 ± 1.7
BP (mmHg)				
Systolic	149 ± 13#	158 ± 15	149 ± 13#	158 ± 13
Diastolic	88 ± 8\$	92 ± 10	89 ± 8\$	92 ± 10
UAE (μg/min)	68.8 ± 42.5	56.3 ± 35.1	68.9 ± 41.6	66.1 ± 39.3
eGFR (MDRD) (mL/min)	74 ± 14	71 ± 14	70 ± 13	72 ± 13
Cholesterol (mg/dL)				
Total	216 ± 41	224 ± 43	230 ± 60	225 ± 43
LDL	137 ± 36	141 ± 33	142 ± 53	140 ± 40
HDL	43 ± 11	44 ± 12	43 ± 12	44 ± 12

Negative concordant indicates no robust (i.e., more than median) response in neither UAE and SBP, and positive concordant indicates no robust (i.e., more than median) response in both parameters. MDRD, Modification of Diet in Renal Disease study equation. *Median UAE response was 18% decline; **median SBP response was 11 mmHg decline; #*P* < 0.001 vs. patients with UAE <median and SBP >median and patients with UAE >median and SBP >median; \$*P* < 0.05 vs. patients with UAE <median and SBP >median and patients with UAE >median and SBP >median.

but not in SBP (discordant SBP response) and 19.3% had a robust reduction in SBP but not in UAE (discordant UAE response).

The baseline characteristics according to UAE and SBP response are shown in Table 2. There were no differences in baseline characteristics except that patients with a robust reduction in SBP, irrespective of the UAE response, had a higher average baseline SBP and diastolic BP compared with patients without robust SBP decline.

Renal outcome

We assessed whether the degree of change in UAE and SBP was associated with a different slope of renal function loss. A larger decrease in UAE during the first 6 months was independently associated with a slower rate of renal function decline during the follow-up time (*P* = 0.0037; Fig. 1). A robust decrease in SBP showed a similar trend of a slower rate of long-term eGFR decline but was not significant (*P* = 0.087).

The rate of eGFR decline according to combined change in UAE and SBP and adjusted for other risk variables is presented in Fig. 2A. A robust UAE reduction resulted in a slower rate of eGFR decline, also in those patients who did not have a robust SBP reduction. The combination of a robust response in UAE and SBP resulted in the lowest rate of progressive renal function loss.

For completeness, we determined the impact of changes in UAE and SBP on the risk for development of overt nephropathy in a secondary analysis. It should be reminded that the initial change in UAE is directly related to the development of overt nephropathy. The risk reduction for development of overt nephropathy was 44% (95% CI 39–59; *P* < 0.001) and 9% (19 to +2; *P* = 0.098) per 50% reduction in UAE and 5 mmHg SBP reduction, respectively. The risk for development of overt nephropathy according to combined change in UAE and SBP and adjusted for other risk variables is presented in Fig. 2B.

CONCLUSIONS—The results of this study show that the response to ARB therapy varies for both UAE and SBP even within the microalbuminuric hypertensive patient. The rate of long-term renal function decline showed a clear dependence on the initial response in UAE irrespective of SBP response. The results of this microalbuminuria study confirm a previous study reporting on proteinuria in which similar individual variations in response to ARB treatment (Losartan) were observed and in which the reduction in proteinuria was independently associated with renal outcome in type 2 diabetic patients with nephropathy (5). Combining the results of that study and the current study, we conclude that monitoring therapy-induced changes in UAE in individual diabetic patients is important in addition to monitoring BP, since therapy-induced changes in both parameters do not run in parallel and both parameters were independently associated with the effectiveness to achieve renal protection.

Table 2—Distribution of the irbesartan and conventional treatment group according to change in albuminuria and SBP from baseline to month 6

	Albuminuria response >median (reduction >18%)			Albuminuria response <median (reduction <18%)			Total (%)
	Quartile 1 (<-50%)	Quartile 2 (-50 to -18%)	Total (%)	Quartile 3 (-18 to +34%)	Quartile 4 (>+34%)	Total (%)	
Irbesartan (N = 353)							
SBP response >median (reduction >11 mmHg)	69 (19.5)	56 (15.9)	35.4	35 (9.9)	33 (9.3)	19.3	55
SBP response <median (reduction <11 mmHg)	40 (11.3)	46 (13)	24.4	45 (12.7)	29 (8.2)	21.0	45
Total (%)			60			40	
Conventional treatment (N = 178)							
SBP response >median (reduction >11 mmHg)	7 (3.9)	17 (9.6)	13.5	21 (11.8)	22 (12.4)	24.2	38
SBP response <median (reduction <11 mmHg)	16 (9.0)	14 (7.9)	16.9	32 (18.0)	49 (27.5)	45.5	62
Total (%)			30			70	

Data are number of patients and (% of total).

The reduction in albuminuria achieved during the initial months of RAAS blockade is a critical step to achieve renoprotection. Trials conducted in populations with and without diabetes showed that agents intervening in the RAAS confer additional renoprotection beyond other antihypertensive regimens. Although in most trials BP control was slightly better in the RAAS treatment arm, the clinical benefit exceeded that which could be attributed to improved BP control (9,15,16). In addition, the reduction in UAE during the initial months of therapy is the most

important determinant of long-term renoprotection. This observation was initially made in diabetic renal disease by Rossing et al. (17) and in nondiabetic renal disease by Apperloo et al. (14) investigating long-term eGFR decline, and later confirmed in analyses from large randomized controlled trials looking at hard renal end points (4,5,7,18). It should be noted that the aforementioned observations are derived from studies enrolling patients with macroalbuminuria (UAE >300 mg/day) and/or eGFR levels below 60 mL/min/1.73 m². Importantly, the results of

the current study extend these findings to the patient population with levels of UAE within the microalbuminuric range (UAE 30–300 mg/day) and eGFR levels above 60 mL/min/1.73 m².

An important question is whether changes in albuminuria can be used as a surrogate end point in clinical trials. The distinct advantage is that trials with surrogate end points require fewer patients, require shorter follow-up, are less expensive, and facilitate drug development. To obtain surrogacy status definitive evidence is required, demonstrating that the surrogate end point is causally related to the clinical end point. It has been pointed out that the evidence for albuminuria as a surrogate end point is reasonably robust in patients with diabetes and macroalbuminuria, but limited data are available in patients with lower UAE (19,20). This study is the first to show that even in the low albuminuria range the initial antialbuminuric response to ARB treatment is an important independent indicator of renoprotection. This suggests that also in patients with microalbuminuria, albuminuria may be a potential candidate as a surrogate end point.

Prospective randomized controlled trials will be necessary to obtain definitive evidence that an approach of targeting UAE confers renoprotection within the microalbuminuria range. These trials should be designed to compare the long-term clinical effect of different predefined UAE targets. Such a design isolates the role of UAE as an independent target for therapy and establishes the clinical relevance of targeting UAE for renal or cardiovascular protection. In this respect, a recent study by Ruggenenti et al. (21) in diabetic and nondiabetic nephropathies compared the

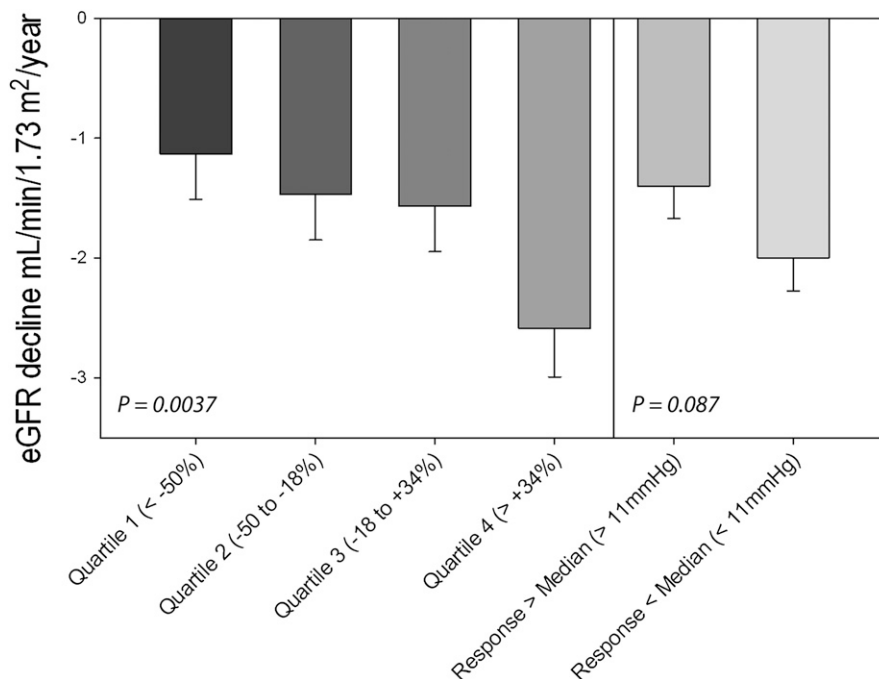


Figure 1—Long-term annual decline in eGFR from 6 to 24 months, per quartile UAE change from baseline to month 6 ($P = 0.0037$) and per group of SBP change from baseline to month 6 (divided over the median change; $P = 0.087$) in 531 type 2 diabetic patients with microalbuminuria.

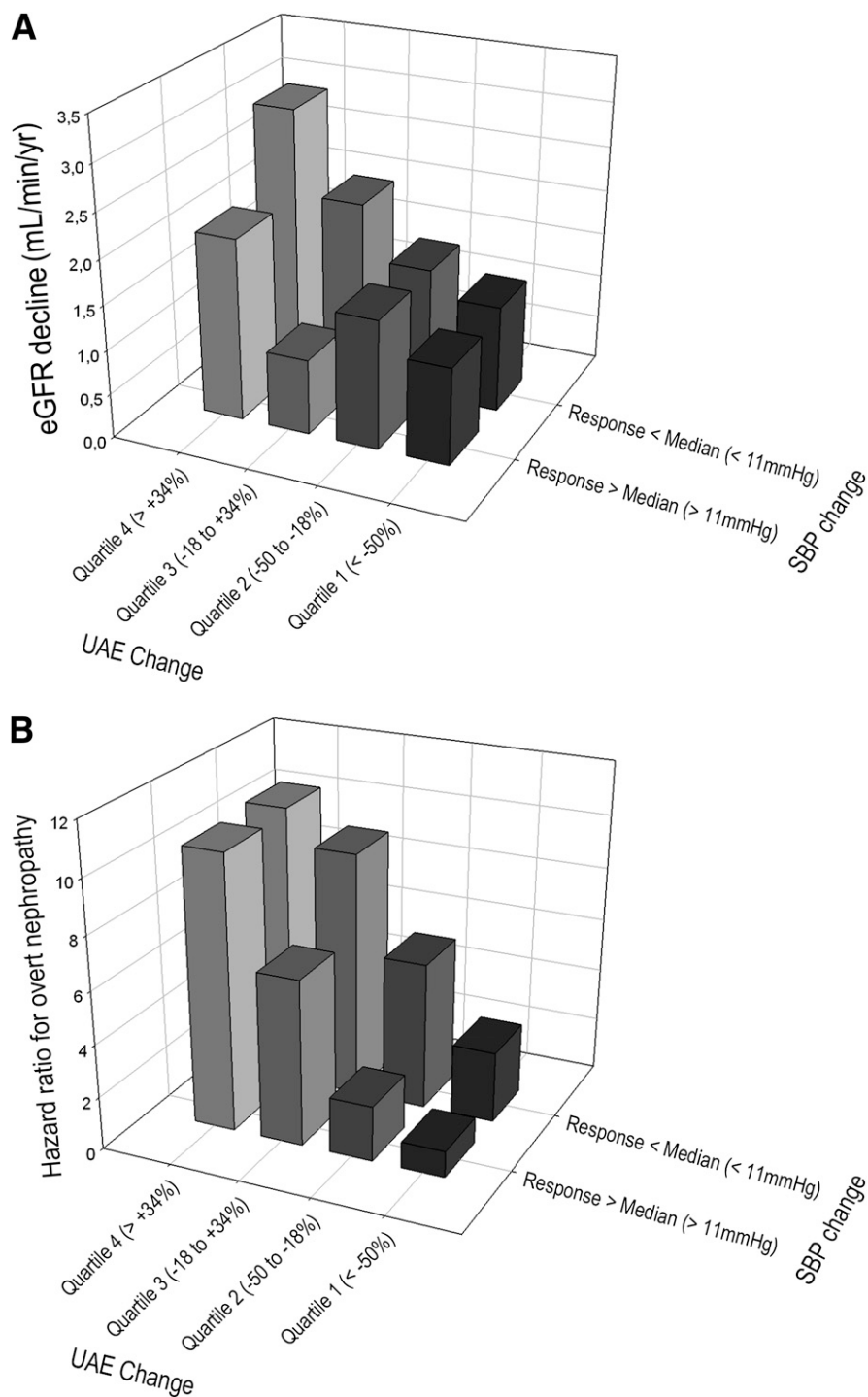


Figure 2—A: Decline in eGFR from 6 to 24 months for groups of UAE and SBP change in 531 type 2 diabetic patients with microalbuminuria. B: Hazard ratios for overt nephropathy from 6 to 24 months for groups of UAE and SBP change in 531 type 2 diabetic patients with microalbuminuria.

efficacy of a treatment strategy specifically targeting UAE with a historical cohort targeting only BP. The results showed that targeting UAE is feasible and translates into substantial risk reductions for end-stage renal disease. Interestingly, again the reduction in UAE was the only variable in

multivariate analyses that was associated with a lower risk of end-stage renal disease. The obvious limitation is that the comparisons published in this report were not randomized. The Renoprotection of Optimal Antiproteinuric Doses (ROAD) study is the only randomized

controlled trial testing a treatment strategy specifically targeting proteinuria. This trial showed that optimal antiproteinuric dosages of RAAS blockade are feasible and resulted in a substantially larger reduction in proteinuria and slower rate of renal function decline in nondiabetic patients (22). Prospective studies confirming these results in diabetic patients with microalbuminuria and proteinuria are needed.

One can only speculate about possible mechanisms underlying the discordant BP and UAE responses. One possibility is that clinical BP and overnight albumin excretion measurements are subject to large random variability and thus do not accurately reflect true BP and UAE. However, patients allocated to irbesartan more often have a robust decline in UAE compared with patients treated with conventional treatment only (60 vs. 30%; Table 1). Hence, a clear difference in discordant response pattern can be deduced, indicating that the ARB treatment responses are not solely due to random variability. Another possible explanation for the discordant treatment responses is that the intraindividual discordance in UAE and SBP response is accounted for by differences in systemic and local RAAS activity or differences in the extent of tissue penetration of RAAS blockade, whereas the SBP response depends on systemic vasculature RAAS inhibition. In support of this hypothesis, preclinical studies have shown that inhibition of extrarenal RAAS plays an important role in mediating BP control (23). However, further research is needed to elucidate the exact mechanisms.

It is noteworthy that this is a post hoc analysis of clinical trial data and the results are no longer based on randomized comparisons. Although we adjusted for a large range of potential confounders, unmeasured confounding may have influenced our results. The results can therefore only be interpreted as hypothesis generating.

In conclusion, our data show that ARB-induced responses in BP and UAE are discordant within a large proportion of patients. This underscores the recommendation of treatment guidelines of diabetes associations to regularly assess both BP and UAE in individual patients with diabetes. Importantly, the response in UAE individually determined renal outcome, regardless of the BP response. This implies that renoprotective strategies

in microalbuminuric patients with type 2 diabetes should not only target BP but also UAE.

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