Efficacy and Safety of Angiotensin II Receptor Blockade in Elderly Patients With Diabetes

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OBJECTIVE — While national guidelines recommend ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy in patients with diabetes and nephropathy, guidelines concerning elderly patients with diabetes have not endorsed these drugs. We sought to assess the nephroprotective efficacy and safety of ARB therapy in elderly patients by conducting age-specific subgroup analyses using data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study.

RESEARCH DESIGN AND METHODS — We studied 1,513 patients with type 2 diabetes and nephropathy who randomly received either losartan or placebo. We tested for effect modification by age of the effect of losartan on the incidence of the predefined end points (doubling of serum creatinine, end-stage renal disease [ESRD], or death) and the risk of adverse events.

RESULTS — Of 1,513 participants, 421 (27.8%) were aged >65 years (maximum age 74 years). Age did not modify the efficacy of losartan in reducing the risk of the primary outcome, a composite of doubling of serum creatinine, ESRD, or death ($P_{interaction} = 0.66$) or its individual components (all $P_{interaction} > 0.44$). In patients aged >65 years, losartan reduced the risk of ESRD by 50% (95% CI 30–81, $P = 0.005$). We found no evidence that older patients were more likely to experience adverse events from losartan such as a rise in serum creatinine or hyperkalemia than younger patients.

CONCLUSIONS — Elderly patients had the same level of benefits and risks as younger patients from treatment with losartan. Underuse of ACEI and ARB therapy in elderly patients because of the perceived lack of efficacy or a greater risk of adverse events appears unjustified.

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In the U.S., the prevalence of diabetes in older adults reaches ~25% in certain ethnic minorities (1) and is continuously increasing (2). In 1988–1994, the prevalence of physician-diagnosed diabetes in all adults aged 60–74 years was 13% but rose to 21% in non-Hispanic blacks and 24% in Mexican Americans (1). Diabetes is one of the most frequent causes of chronic kidney disease (CKD) and the single largest reason for initiation of renal replacement therapy. In 1980, diabetes was the cause of end-stage renal disease (ESRD) in only 13% of new patients. Twenty years later, however, it was the primary renal diagnosis in 55–64% of Hispanic ESRD patients and 43% of non-Hispanic ESRD patients (3). Most incident ESRD patients in the U.S. are aged >64.5 years at initiation of renal replacement therapy. By 2030, almost 60% of the projected 2.24 million ESRD patients are expected to have diabetes and more than half of those will be aged ≥65 years (3). Thus, the renal consequences of diabetes constitute a substantial burden in both clinical and economic terms, especially for the elderly.

Clinical trials have identified several modifiable factors that determine the rate of progression of CKD (4–7). Treatment with ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to be efficacious in reducing the rate of progression of CKD, both in patients with type 1 diabetes and in those with type 2 diabetes (8–12). Several professional societies have developed clinical practice guidelines that recommend use of these inhibitors of the renin-angiotensin-aldosterone system (RAAS) in patients with diabetes with microalbuminuria or more pronounced proteinuria or as first-line treatment in those with hypertension (13, 14). However, prevention of nephropathy is not a focus in the "Guidelines for Improving the Care of the Older Person with Diabetes Mellitus," published by the American Geriatrics Society (15), even though the elderly represent the single most important demographic group initiating renal replacement therapy (3). There is sparse evidence to support or refute this therapeutic approach in the elderly. We therefore studied the effect of age on the renoprotective efficacy and safety of the angiotensin II receptor antagonist, losartan, in elderly patients, using primary data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study (11).

RESEARCH DESIGN AND METHODS

— The RENAAL study was a multinational, randomized, place-

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Abbreviations: ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; ESRD, end-stage renal disease; RAAS, renin-angiotensin-aldosterone system; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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bo-controlled trial designed to evaluate the renoprotective efficacy of losartan in patients with type 2 diabetes. A total of 1,513 patients from 250 centers in 28 countries in Asia, Europe, Central America, South America, and North America participated in the study. After a 6-week screening phase, patients were randomized to either 50 mg losartan (titrated to 100 mg as needed) or placebo. Additional antihypertensive medications were permitted (calcium channel blockers, β-blockers, centrally acting agents, and diuretics but not ACEIs or ARBs) in order to reach the goal blood pressure <140/90 mmHg. Patients were followed for a mean of 3.4 years (range 2.3–4.6). The detailed study design and the main analyses have been published elsewhere (11,16). Using the full study cohort of 1,513 randomized patients, we stratified patients into three groups according to tertiles of their age at study baseline: ≤57, >57 to 65, and >65 years. All subsequent analyses were conducted based on these age strata. For each age-group, we summarized all baseline characteristics using counts and percentages (categorical variables) or means ± SD (continuous variables).

End points

We used the end points specified for the main analysis of the RENAAL study (16). The primary end point was a composite of a doubling of the serum creatinine concentration (from study baseline, confirmed by a second measurement ≥4 weeks after the first doubling), ESRD, or death. Other end points studied were each of these separately, as well as two-way combinations.

Adverse events

Adverse events were evaluated by combining clinical and laboratory adverse events. Adverse events and serious adverse events were classified in accordance with regulatory definitions (17). Since early adverse events of ARBs (e.g., hyperkalemia, increase in serum creatinine) have been of particular concern in elderly patients (18,19), we specifically assessed their occurrence within the first 14 and 30 days after randomization. We also measured the proportion of patients who discontinued the study drug during the trial.

Statistical analyses

The intention-to-treat approach was used for time-to-event analysis in which all randomized patients were included regardless of discontinuation of the study drug. Primary outcomes were summarized by treatment group and age category using the number of events per 1,000 patient years of follow-up. The effect of losartan versus placebo was assessed in each age subgroup using both prespecified primary analysis and adjusted analysis, as specified in the data analysis plan. The main hypothesis test for interaction between age and treatment group was evaluated using the Wald test. For the primary analysis, the Cox regression model included treatment group and geographic region as covariates and baseline proteinuria level (i.e., urine albumin-to-creatinine ratio <2,000 vs. ≥2,000 mg/g) as a hazard stratum. For the adjusted analysis, the Cox regression model included treatment group and the four baseline covariates that had been shown to predict the primary outcome in RENAAL: proteinuria, serum creatinine, serum albumin, and whole blood hemoglobin (20). These adjusted analyses corrected for the accidental imbalances in baseline proteinuria in the RENAAL study, which occurred despite block randomization by proteinuria (<2,000 vs. ≥2,000 mg/g). Since the effectiveness of randomization in equally allocating characteristics across randomization groups declines with smaller sample size, we further adjusted age-specific subgroup analyses for other baseline variables that predicted ESRD in the RENAAL study (20). Independent of possible imbalances in baseline variables across treatment groups, inclusion of prognostic variables in the analyses of randomized trial data can increase statistical efficiency, and the clinically most relevant subject-specific measure of treatment effect can be approximated (21).

Due to insufficient power for each stratum-specific analysis, the objective for subgroup analyses is to look for consistent treatment effects rather than efficacy in subgroups, especially when the overall study was significant (22). Thus, tests for interaction were conducted by adding dummy covariates for the three age categories and multiplicative interaction terms for treatment group by age category in the full cohort model. We used the SAS software package (version 8) for all analyses. All tests were two sided and used a statistical significance threshold of $P < 0.05$.

RESULTS

— The study population of 1,513 patients has been described previously (11). Of these, 505 (33.4%) were aged ≤57 years at enrollment into the trial, 587 (38.8%) were aged between 57 and 65 years, and 421 (27.8%) were aged >65 years; the oldest participant was aged 74 years at study baseline. The age-group of particular interest, patients aged >65 years, was predominantly comprised of men (64.8%) and individuals of white race (57.5%). Table 1 provides all baseline characteristics separately for each age stratum. Older participants in the RENAAL study were more likely to be white, less likely to be smokers, and more likely to have a history of angina or past myocardial infarction. Older patients tended to be leaner and to have a higher systolic, but lower diastolic, blood pressure. Their estimated glomerular filtration rate was lower despite no difference in serum creatinine concentrations. Several other laboratory measurements, such as serum albumin, urine albumin-to-creatinine ratio, HbA_{1c}, serum uric acid, and several lipid marker concentrations, were slightly more favorable in older than in younger patients (Table 1).

Primary study end point

In intention-to-treat analyses of the primary end point, the time to doubling of baseline serum creatinine, ESRD, or death, the *P* value for interaction was 0.349 in unadjusted and 0.662 in adjusted analyses (Table 2), each supporting the null hypothesis that the treatment effect of losartan on the primary outcome did not differ by age. In age-stratified analyses, losartan reduced the rate of the primary end point by 11% in patients aged ≤57 years (hazard ratio [HR] 0.89 [95% CI 0.69–1.15]), by 27% in those aged >57–65 years (0.73 [0.58–0.94]), and by 4% in patients aged >65 years (0.96 [0.71–1.21]) compared with placebo recipients (Table 2). Adjustment for other baseline characteristics changed these findings somewhat: 20% (0.80 [0.61–1.04]), 32% (0.68 [0.53–0.87]), and 23% (0.77 [0.57–1.05]), respectively.

Secondary study end points

Similar to the analyses of the primary end point, there was no indication for modification of the treatment effect by age for the combined outcomes of doubling of serum creatinine or ESRD ($P_{interaction}$ = 0.605), ESRD or death ($P_{interaction}$ = 0.728), or the individual outcomes of

Table 1—*Patient characteristics at baseline, by age-group*

	Age ≤57 years		Age >57 to 65 years		Age >65 years		
	n	Count (%) or means ± SD	*n*	Count (%) or means ± SD	*n*	Count (%) or means ± SD	*P*
Demographic and baseline variables							
Sex							
Female	505	171 (33.9)	587	238 (40.5)	421	148 (35.2)	
Male	505	334 (66.1)	587	349 (59.5)	421	273 (64.8)	0.408
Race							
Asian	505	100 (19.8)	587	84 (14.3)	421	68 (16.2)	0.070
Black	505	88 (17.4)	587	92 (15.7)	421	50 (11.9)	0.026
Hispanic	505	108 (21.4)	587	111 (18.9)	421	58 (13.8)	0.004
White	505	199 (39.4)	587	294 (50.1)	421	242 (57.5)	<0.001
Smoking	504	121 (24.0)	585	90 (15.4)	420	62 (14.8)	<0.001
Medical History							
Amputation	505	52 (10.3)	587	56 (9.5)	421	27 (6.4)	0.056
Anemia	505	117 (23.2)	587	132 (22.5)	421	80 (19.0)	0.160
Angina	505	26 (5.1)	587	57 (9.7)	421	58 (13.8)	<0.001
Lipid disorder	505	188 (37.2)	587	209 (35.6)	421	152 (36.1)	0.670
Myocardial infarction	505	47 (9.3)	587	77 (13.1)	421	69 (16.4)	0.001
Neuropathy	505	263 (52.1)	587	286 (48.7)	421	208 (49.4)	0.346
Retinopathy	505	336 (66.5)	587	372 (63.4)	421	259 (61.5)	0.105
Revascularization	505	1 (0.2)	587	1 (0.2)	421	0 (0.0)	0.451
Stroke	505	0 (0.0)	587	1 (0.2)	421	0 (0.0)	0.822
Laboratory results and vital statistics							
BMI (kg/m^2)	493	30.7 ± 7.2	575	29.6 ± 5.9	410	28.7 ± 5.4	<0.001
Systolic blood pressure (mmHg)	505	149.3 ± 18.3	587	153.9 ± 19.6	421	154.4 ± 19.7	<0.001
Diastolic blood pressure (mmHg)	505	85.5 ± 10.2	587	81.3 ± 10.1	421	80.2 ± 10.3	<0.001
Serum albumin (g/dl)	498	3.7 ± 0.5	577	3.8 ± 0.4	412	3.9 ± 0.4	<0.001
Urine albumin-to-creatinine ratio	505	2,080 ± 1,836	587	1,765 ± 1,685	421	1,541 ± 1,465	<0.001
Geometric mean	505	1,396.7	587	1,118.7	421	977.6	<0.001
Serum creatinine (mg/dl)	505	1.9 ± 0.5	587	1.9 ± 0.5	421	1.9 ± 0.5	0.811
Estimated GFR (ml/min per 1.73 m^2)	505	41.4 ± 12.8	587	39.2 ± 11.7	421	38.8 ± 12.6	0.001
HbA_{1c} (%)	497	8.7 ± 1.7	583	8.5 ± 1.6	416	8.3 ± 1.5	<0.001
Total cholesterol (mg/dl)	500	235.5 ± 59.1	582	227.8 ± 53.5	416	219.4 ± 52.5	<0.001
HDL cholesterol (mg/dl)	495	45.3 ± 15.4	581	44.2 ± 14.2	415	46.0 ± 15.7	0.657
LDL cholesterol (mg/dl)	435	146.9 ± 48.7	530	142.3 ± 44.6	394	136.9 ± 43.5	0.002
Hemoglobin (g/dl)	490	12.4 ± 1.9	567	12.5 ± 1.8	411	12.7 ± 1.7	0.103
Serum triglycerides (mg/dl)	500	246.7 ± 254.2	582	216.1 ± 154.5	416	189.8 ± 132.6	<0.001
Geometric mean	500	191.1	582	182.5	416	162.9	<0.001
Serum uric acid (mg/dl)	505	6.9 ± 1.8	587	6.7 ± 1.6	421	6.5 ± 1.6	<0.001

doubling of serum creatinine ($P_{interaction}$ = 0.448), death ($P_{interaction}$ = 0.695), or ESRD ($P_{interaction}$ = 0.556). While tests for interaction were the focus of analysis, some stratum-specific results deserve mention: while angiotensin II receptor blockade did not reduce mortality in either the overall study or in any of the age strata, the adjusted risk of ESRD was significantly reduced in all age-groups. Among patients aged >65 years, the risk of ESRD was reduced by exactly 50% (HR 0.50 [95% CI 0.30–0.81], P = 0.005), which was highly significant even in this relatively small study sample. Similarly, there was a 38% event-rate reduction regarding doubling of serum creatinine among the oldest patients, which closely approached statistical significance despite the small sample size of this group (0.62 [0.38–1.01], P = 0.057).

In evaluating aggregate rates of adverse events, the data revealed that these did not differ between patients randomized to losartan versus placebo (Table 3). As before, none of the tests for interaction between losartan and age were significant, indicating that older patients were no more susceptible to experiencing adverse events from losartan than were younger patients.

We next focused on specific adverse events that had been cited as particular concerns regarding inhibition of the RAAS in the elderly: rise in serum creatinine concentration and hyperkalemia. A rise in serum creatinine appeared to be less frequent with more advanced age. There was no indication that this adverse event was more frequent in patients on losartan than on placebo (Table 4). By contrast, losartan was clearly associated with a greater rate of hyperkalemia, but this effect was present in all age strata. The nonsignificant P value for interaction (0.402) indicated that age did not increase the risk of hyperkalemia from losartan. Other adverse events such as

Table 2—*Effect of losartan on study outcomes, by age-group*

	Losartan		Placebo		Primary*			Adjusted†		
Age category	*n*	*K* (rate)	*n*	*K* (rate)	HR (95% CI)	*P*	$P_{interaction}$	HR (95% CI)	*P*	$P_{interaction}$
Primary end point (DsCr/ESRD/death)										
All patients	751	327 (159.3)	762	359 (180.7)	0.84 (0.72–0.98)	0.022		0.74 (0.63–0.87)	<0.001	
≤57 years	259	119 (174.1)	246	122 (196.5)	0.89 (0.69–1.15)	0.365		0.80 (0.61–1.04)	0.089	
>57 to ≤65 years	288	124 (155.7)	299	144 (185.3)	0.73 (0.58–0.94)	0.012		0.68 (0.53–0.87)	0.003	
>65 years	204	84 (146.5)	217	93 (158.1)	0.96 (0.71–1.29)	0.762	0.349	0.77 (0.57–1.05)	0.095	0.662
DsCr/ESRD										
All patients	751	226 (110.1)	762	263 (132.4)	0.79 (0.66–0.94)	0.010		0.68 (0.57–0.82)	<0.001	
≤57 years	259	93 (136.0)	246	102 (164.3)	0.84 (0.64–1.12)	0.238		0.75 (0.56–1.00)	0.048	
>57 to ≤65 years	288	84 (105.5)	299	103 (132.5)	0.68 (0.51–0.91)	0.009		0.60 (0.44–0.82)	0.001	
>65 years	204	49 (85.5)	217	58 (98.6)	0.88 (0.60–1.29)	0.522	0.450	0.69 (0.46–1.03)	0.066	0.605
ESRD/death										
All patients	751	255 (117.2)	762	300 (141.3)	0.80 (0.68–0.95)	0.009		0.72 (0.61–0.86)	<0.001	
≤57 years	259	90 (121.9)	246	98 (144.4)	0.87 (0.65–1.16)	0.345		0.78 (0.58–1.05)	0.108	
>57 to ≤65 years	288	96 (113.8)	299	122 (146.4)	0.70 (0.53–0.91)	0.008		0.66 (0.50–0.88)	0.004	
>65 years	204	69 (116.0)	217	80 (131.0)	0.93 (0.68–1.29)	0.682	0.333	0.71 (0.50–0.99)	0.043	0.728
DsCr										
All patients	751	162 (78.9)	762	198 (99.7)	0.75 (0.61–0.92)	0.006		0.64 (0.52–0.80)	<0.001	
≤57 years	259	74 (108.2)	246	79 (127.3)	0.85 (0.61–1.16)	0.302		0.74 (0.53–1.03)	0.072	
>57 to ≤65 years	288	59 (74.1)	299	79 (101.6)	0.61 (0.43–0.86)	0.005		0.54 (0.38–0.78)	0.001	
>65 years	204	29 (50.6)	217	40 (68.0)	0.73 (0.45–1.18)	0.196	0.397	0.62 (0.38–1.01)	0.057	0.448
ESRD										
All patients	751	147 (67.5)	762	194 (91.4)	0.71 (0.58–0.89)	0.002		0.62 (0.49–0.77)	<0.001	
≤57 years	259	62 (84.0)	246	78 (114.9)	0.77 (0.55–1.08)	0.132		0.68 (0.48–0.97)	0.031	
>57 to ≤65 years	288	53 (62.8)	299	72 (86.4)	0.62 (0.44–0.89)	0.010		0.57 (0.39–0.83)	0.004	
>65 years	204	32 (53.8)	217	44 (72.0)	0.79 (0.50–1.25)	0.318	0.625	0.50 (0.30–0.81)	0.005	0.556
Death										
All patients	751	158 (68.0)	762	155 (66.4)	1.02 (0.81–1.27)	0.884		0.99 (0.79–1.24)	0.921	
≤57 years	259	45 (55.4)	246	35 (45.8)	1.18 (0.75–1.83)	0.475		1.16 (0.74–1.83)	0.516	
>57 to ≤65 years	288	61 (68.3)	299	68 (74.1)	0.91 (0.64–1.28)	0.576		0.90 (0.63–1.30)	0.581	
>65 years	204	52 (84.3)	217	52 (79.7)	1.12 (0.76–1.64)	0.570	0.596	0.99 (0.66–1.46)	0.943	0.695

Analysis was done separately by each age stratum. *K* (rate), number of events per 1,000 patient years of follow-up. $P_{interaction}$, *P* value for interaction between treatment effect and age stratum. *Multivariate Cox model with treatment group and region as covariates and baseline proteinuria level (< or ≥2,000) as strata. †Multivariate Cox model with treatment group and region as covariates and additional baseline covariates of proteinuria, serum albumin, serum creatinine, and hemoglobin. DsCr, doubling of serum creatinine.

anemia or hypoglycemia were similar between losartan and placebo, the latter being important due to the increased risk of hypoglycemia that had been reported for ACEI therapy (23,24). Age was not a modifying factor for the risk of adverse events (Table 4).

CONCLUSIONS — This study provides the best evidence to date supporting use of drugs that block the RAAS in the elderly. Using original data from the RENAAL study, a large trial of the efficacy of ARB therapy on renal end points in patients with type 2 diabetes, we found no indication that the effectiveness of losartan treatment differed by age. Further, in adjusted analyses restricted to the 421 patients aged >65 years, losartan significantly reduced the event rate of ESRD by 50% compared with placebo. Similarly, the rate of doubling of baseline serum creatinine in these elderly patients was reduced by 38% with losartan treatment. Analyses of adverse event rates revealed no evidence that age increased the risk of important side effects from losartan therapy. The only adverse event that was more frequent in patients on losartan was hyperkalemia, but this increased risk was present in all age strata. The *P* value for interaction was 0.40, indicating that older patients were not more prone to develop this side effect from losartan therapy. This provides evidence that losartan treatment is equally efficacious and carries no greater risk than in younger patients with type 2 diabetes. Thus, while these stratum-specific HRs or event rates are numerically different, a nonsignificant interaction term indicates that the effects in the three subgroups are not different from each other regardless of whether some are not significant individually.

The evidence from this study is particularly important in light of the underuse of therapeutic RAAS blockade, especially in elderly patients with diabetes. A recent study of Medicare beneficiaries in two eastern states of the U.S. found that as recently as in 2003, only half of therapy-dependent diabetic subjects with hypertension and/or proteinuria received ACEI or ARB treatment (25). In that study, age was a powerful and independent predictor of lower use of these medications. In comparison with patients aged between 65 and 74 years, patients aged 75–84 years were 8% (95% CI 2–14) less likely to receive ACEI or ARB therapy and patients aged ≥85 years were 30% (24–35) less likely (25). Among relatively younger patients enrolled in a large western U.S. HMO, 54% of patients with albuminuria, 64% of patients with hypertension, and 74% of patients with

Table 3—*Effect of losartan on discontinuation and adverse events, by age-group*

	Losartan		Placebo			
	n	Count (%)	*n*	Count (%)	*P*	$P_{interaction}$
Discontinuation						
≤57 years	259	113 (43.6)	246	128 (52.0)	0.059	
>57 to ≤65 years	288	131 (45.5)	299	156 (52.2)	0.105	
>65 years	204	100 (49.0)	217	119 (54.8)	0.232	0.921
All adverse events						
Entire follow-up						
≤57 years	259	247 (95.4)	246	234 (95.1)	0.897	
>57 to ≤65 years	288	276 (95.8)	299	290 (97.0)	0.451	
>65 years	204	199 (97.5)	217	211 (97.2)	0.840	0.762
First 14 days						
≤57 years	259	90 (34.7)	246	98 (39.8)	0.237	
>57 to ≤65 years	288	91 (31.6)	299	82 (27.4)	0.268	
>65 years	204	62 (30.4)	217	61 (28.1)	0.607	0.242
First 30 days						
≤57 years	259	130 (50.2)	246	124 (50.4)	0.962	
>57 to ≤65 years	288	135 (46.9)	299	128 (42.8)	0.322	
>65 years	204	86 (42.2)	217	84 (38.7)	0.471	0.752
Serious adverse events						
Entire follow-up						
≤57 years	259	153 (59.1)	246	149 (60.6)	0.732	
>57 to ≤65 years	288	179 (62.2)	299	195 (65.2)	0.440	
>65 years	204	151 (74.0)	217	145 (66.8)	0.106	0.191
First 14 days						
≤57 years	259	3 (1.2)	246	5 (2.0)	0.432	
>57 to ≤65 years	288	7 (2.4)	299	2 (0.7)	0.082	
>65 years	204	5 (2.5)	217	6 (2.8)	0.840	0.174
First 30 days						
≤57 years	259	6 (2.3)	246	9 (3.7)	0.375	
>57 to ≤65 years	288	17 (5.9)	299	8 (2.7)	0.053	
>65 years	204	8 (3.9)	217	9 (4.1)	0.906	0.135

Both clinical and laboratory adverse experiences were considered using the on-treatment approach, i.e., only adverse events that occurred during the double-blinded period plus 14 days were included in the summary. Although a patient may have had two or more adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories. *P* values were calculated to compare proportions between two treatment groups using the χ^2 test, and $P_{interaction}$ between treatment group and age category were calculated using the Breslow-Day test for homogeneity of the ORs.

both albuminuria and hypertension received ACEI or ARB therapy in 2000 (26). In light of the available evidence, underuse of these medications may be partly responsible for the high rates of renal replacement therapy in the elderly, incurring substantial opportunity costs for society overall. In a recent economic evaluation, Rosen et al. (27) demonstrated that providing free ACEI therapy to all elderly Medicare beneficiaries with diabetes would be a highly cost-effective strategy because it extended life and would actually result in substantial societal cost savings.

Several factors may be responsible for the underuse of RAAS blockade in elderly patients with diabetes. Health care providers may be hesitant to prescribe ACEI or ARB to these patients for several reasons. One reason might be the perception that the risk-benefit ratio of such therapies is unfavorable in the elderly because they are at greater risk of adverse events from these treatments. Whether this is actually the case is unclear. Age was not a predictor of hyperkalemia in patients using ACEI at a U.S. renal clinic (28). Another cause of underprescribing may be some physicians' perception that the reduced life expectations of elderly patients with diabetes and the time delay until the benefits from such therapies become apparent warrant prioritization of other treatment strategies with more immediate benefits. The present analysis clearly demonstrates that this is a wrong perception and that even elderly patients benefit greatly from ARB treatment. Finally, the absence of compelling evidence of the benefits and risks associated with RAAS blockade in the elderly may have been a factor. It appears that all these components helped produce a rather subdued endorsement of ACEI or ARB treatment in published practice guidelines for the treatment of elderly patients with diabetes (15). While these guidelines included a recommendation that "a test for the presence of microalbumin should be performed at diagnosis" and annually thereafter, there is no treatment recommendation in case of a positive test result. By contrast, in the hypertension section of the guidelines, it is mentioned that "data from several uncontrolled studies suggest that older adults are more susceptible to the reduction in renal function that are related to ACE inhibitors" (15). However, the cited reference does not provide any compelling evidence to support this claim (29). The present study provides evidence to the contrary, that such reserva-

Table 4—*Effect of losartan on selected adverse events, by age-group*

	Losartan		Placebo			
	n	Count (%)	*n*	Count (%)	*P*	$P_{interaction}$
Rise in serum creatinine						
Entire follow-up						
≤57 years	259	63 (24.3)	246	53 (21.5)	0.458	
>57 to ≤65 years	288	47 (16.3)	299	60 (20.1)	0.240	
>65 years	204	27 (13.2)	217	28 (12.9)	0.920	0.388
First 14 days						
≤57 years	259	1 (0.4)	246	1 (0.4)	0.971	
>57 to ≤65 years	288	0 (0.0)	299	0 (0.0)	—	
>65 years	204	0 (0.0)	217	0 (0.0)	—	—
First 30 days						
≤57 years	259	4 (1.5)	246	3 (1.2)	0.755	
>57 to ≤65 years	288	0 (0.0)	299	1 (0.3)	0.326	
>65 years	204	0 (0.0)	217	2 (0.9)	0.169	0.266
Hyperkalemia						
Entire follow-up						
≤57 years	259	69 (26.6)	246	27 (11.0)	0.000	
>57 to ≤65 years	288	74 (25.7)	299	46 (15.4)	0.002	
>65 years	204	40 (19.6)	217	21 (9.7)	0.004	0.402
First 14 days						
≤57 years	259	6 (2.3)	246	2 (0.8)	0.176	
>57 to ≤65 years	288	6 (2.1)	299	2 (0.7)	0.140	
>65 years	204	3 (1.5)	217	1 (0.5)	0.286	0.996
First 30 days						
≤57 years	259	11 (4.2)	246	2 (0.8)	0.015	
>57 to ≤65 years	288	8 (2.8)	299	5 (1.7)	0.363	
>65 years	204	4 (2.0)	217	2 (0.9)	0.369	0.455
Anemia						
Entire follow-up						
≤57 years	259	46 (17.8)	246	39 (15.9)	0.567	
>57 to ≤65 years	288	51 (17.7)	299	39 (13.0)	0.117	
>65 years	204	37 (18.1)	217	29 (13.4)	0.178	0.749
First 14 days						
≤57 years	259	0 (0.0)	246	0 (0.0)	—	
>57 to ≤65 years	288	2 (0.7)	299	1 (0.3)	0.541	
>65 years	204	0 (0.0)	217	0 (0.0)	—	—
First 30 days						
≤57 years	259	2 (0.8)	246	0 (0.0)	0.167	
>57 to ≤65 years	288	4 (1.4)	299	2 (0.7)	0.386	
>65 years	204	2 (1.0)	217	0 (0.0)	0.144	0.444
Hypoglycemia						
Entire follow-up						
≤57 years	259	35 (13.5)	246	27 (11.0)	0.385	
>57 to ≤65 years	288	46 (16.0)	299	37 (12.4)	0.211	
>65 years	204	31 (15.2)	217	29 (13.4)	0.591	0.923
First 14 days						
≤57 years	259	3 (1.2)	246	1 (0.4)	0.341	
>57 to ≤65 years	288	3 (1.0)	299	2 (0.7)	0.623	
>65 years	204	3 (1.5)	217	2 (0.9)	0.603	0.903
First 30 days						
≤57 years	259	3 (1.2)	246	2 (0.8)	0.695	
>57 to ≤65 years	288	4 (1.4)	299	5 (1.7)	0.780	
>65 years	204	4 (2.0)	217	2 (0.9)	0.369	0.672

Both clinical and laboratory adverse experiences were considered using the on-treatment approach, i.e., only adverse events which occurred during the double-blinded period plus 14 days were included in the summary. Although a patient may have had two or more adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories. *P* values were calculated to compare proportions between two treatment groups using the χ^2 test, and $P_{interaction}$ between treatment group and age category were calculated using the Breslow-Day test for homogeneity of the ORs. Study protocol terms used to define adverse events: renal failure as "acute renal failure," "renal failure," "chronic renal failure," "renal insufficiency," or "ESRD"; rise in creatinine as "serum creatinine increased" or "creatinine clearance decreased"; hyperkalemia as "hyperkalemia"; anemia as "anemia," "anemia of uremia," "hemolytic anemia," "microcytic anemia," or "lab hemoglobin decreased"; and hypoglycemia as "hypoglycemia" or "blood glucose abnormality."

tion toward recommending RAAS blockade may be unjustified. In addition to physicians' caution in prescribing RAAS blockade in the elderly, an alternative explanation for the observed low use of these medications in the elderly may be low patient adherence to prescribed ACEI or ARB treatment. We know of no studies of primary filling rates of prescribed ACEI or ARB medication or of long-term persistence with these regimens.

This study has certain limitations. While the patients enrolled in the RENAAL study represented a diverse patient mix regarding origin, ethnicity, and comorbidity pattern, it is uncertain whether both effectiveness and risks associated with losartan as observed in elderly participants in the RENAAL study can be generalized to older patients in a more typical care setting. The tight monitoring schedule of a clinical trial may not reflect the surveillance environment present in typical practice setting, but it can provide important information about adverse events. Hence, the results from the analyses of adverse event rates provide particularly important information for medical decision making regarding RAAS blockade. Further, the oldest patient in the RENAAL study was 74 years at study onset; it is uncertain whether we can extrapolate the findings from this study to very old patients. Finally, while we used the statistical test that maximized power to detect interactions with age, limited power may have been an alternative explanation for nonrejection of the null hypotheses of no interaction.

In conclusion, we have provided important information for the clinician who faces the challenge of treating an elderly patient with diabetes. We find that even in older individuals, the effectiveness and safety of losartan treatment is no different from younger patients, when administered and monitored appropriately. Thus, from a physician's perspective, renoprotection via RAAS blockade should be a mandatory component of comprehensive diabetes care in elderly patients with nephropathy. From a policy maker's perspective, further dissemination of these renoprotective treatments, especially in the elderly, appears to be an important goal that could be accomplished by removing economic barriers to such treatment by adding ACEI or ARB treatment in diabetic subjects to the growing list of quality-of-care indicators or by implementing both. Attaining adequate RAAS blockade is likely to be beneficial for the individual patient, as well as yielding savings in health care costs, especially in light of the increasing numbers of seniors, the rising incidence of diabetes among the elderly, and the catastrophic consequences of end-stage kidney disease, particularly in older patients with diabetes.

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